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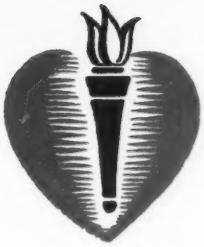

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Editorial

Acquired or Inherited Factors in Cardiovascular Disease

NO MOTHER enjoys the prospect that her solicitous ministrations will be of little avail and that the behavior of her offspring stems inevitably from predetermined influences. Similarly, many physicians resist the thought that some disorders of unknown etiology might be considered as inborn errors rather than the result of environmental factors subject to manipulation.

The operation of a gun clearly requires a charge of powder as well as a firing pin. In the case of some diseases, there is both an undeniable susceptibility or "tendency" as well as a "trigger." Examples might be the recrudescence of gout after dietary indiscretion or a surgical procedure, but always in the setting of an underlying disturbance in uric acid metabolism; or the initial appearance or exacerbation of diabetes mellitus after a host of noxious stimuli, but often superimposed upon an already existent biochemical defect.

Relationships in some areas are more obscure. Emotional factors "trigger" many a peptic ulcer, yet factors of susceptibility assuredly play some part, even though ill defined. If there be a trend, it is that the pattern of an increasing number of illnesses obliges us to look backwards to points far distant from the onset of the overt explosion. Witness the higher incidence of schizophrenia in the identical twin of an affected individual, the rarity of involvement in both of two nonidentical twins! Or consider disseminated lupus erythematosus, in which a biologically false-positive serologic reaction may antedate the outward manifestations of disease by many years!

Atherosclerosis and hypertension are highly prevalent conditions. Among the outside agents and environmental factors that have been submitted as having a possible bearing on their origin are psychologic influences, physical activity, occupation, income, diet, altitude, climate, geography, tobacco, caffeine, infectious agents, and heavy metals, to mention but a few. Despite the voluminous literature on the subject, in no instance has the validity of any one of these claims been substantiated to the exclusion of other variables. Even alleged variations in prevalence based on studies of different nationalities and races need further confirmation. On last analysis, the apparent prevalence of atherosclerosis and hypertension is based on inadequate methods of clinical identification or arbitrary criteria of definition; with the exception of differences related to age, sex, and possibly race, no valid observations have been established.[1]

Because of our limited knowledge, the possibility should not be dismissed that hereditary factors leading to variations in individual susceptibility may be all important. There are strong clues provided by the suggestion that the constitutional type may be of significance in relation to the development of atherosclerosis,[2] that primary hypertension is at least a familial disorder.[3] One is apt to overlook the possibility of "tendency" if broad population samples are studied as a single unit. Should there be but a segment that is susceptible through some inborn error, then it would be both unwise and unnecessary to emphasize the environment or apply preventative measures for all of mankind.

It is erroneous to feel that an inherited tendency implies no possibility for understanding or change, and no effective treatment. A "built-in" tendency still implies a difference greater than that incorporated into the gene, for to create a disorder it must be expressed ultimately in some alteration of cellular structure or function, some abnormal metabolic activity or end-organ response.

The technics of epidemiologic research should be no different from those employed in the experimental laboratory. There is just as great a need for accurate methodology, careful control, and painstaking detail. Often the simple, well-planned, "yes-or-no" study will yield the most definitive evidence. Rather than more extensive, loosely conceived investigations, more fruitful study might be conducted along the lines of small identifiable groups with a known predisposition to disease. For example, food-faddists might provide a natural method of delineating dietary factors; inquiry into the incidence of disease among adopted children might separate genetic from familial factors. It is necessary to narrow one's sights to clearly defined population groups.

Many hypotheses have been introduced, few have been validated, and only rarely have all the other variables been excluded. Before proceeding further along diverse paths, let us take our bearings and settle a basic question on which all future orientation depends—Which is more important in the etiology of atherosclerosis and hypertension, "trigger or tendency"?

GEORGE A. PERERA

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Hypertensive Pulmonary Vascular Disease

By DONALD HEATH, M.D., AND WILLIAM WHITAKER, M.D., B.Sc., M.R.C.P.

Patients with pulmonary artery blood pressures that are chronically elevated to levels of the order of the systemic blood pressures, form a distinct clinicopathologic entity. This condition may complicate a ventricular septal defect, Eisenmenger's complex, patent ductus arteriosus, atrial septal defect, and mitral stenosis, and it may occur as idiopathic pulmonary hypertension. The clinical picture is dominated by symptoms and signs characteristic of pulmonary hypertension, which often mask underlying cardiac anomalies, and definitive pathologic changes occur in the pulmonary vasculature. The term hypertensive pulmonary vascular disease is therefore suggested for this distinct group of patients.

APPLYING Forssman's[1] method of cardiac catheterization, Dexter and his co-workers[2] showed that the tip of the cardiac catheter could be safely introduced into the pulmonary artery to obtain direct records of pulmonary artery blood pressure. This technic has been used by many observers to study pulmonary artery blood pressures in congenital and acquired heart disease and in parenchymal lung disease. It has been found that the arterial blood pressures in the lesser circulation occasionally approached or exceeded those in the systemic circulation in patients with mitral stenosis,[3-6] with patent ductus arteriosus,[7-14] with Eisenmenger's complex,[15-19] with ventricular septal defects,[16, 20] with atrial septal defects,[16] and with idiopathic pulmonary hypertension.[21-23] In the reports of these patients with a great increase in pulmonary vascular resistance the striking features were due to pulmonary arterial hypertension that dominated the clinical picture and often masked an underlying cardiac lesion. Wood[22] and Cutler and his associates[24] noted a similarity among patients with a great increase in pulmonary vascular resistance and recognized that severe pulmonary hypertension produced a characteristic clinical syndrome. The histologic appearances of pulmonary blood vessels associated with severe pulmonary arterial hypertension have been described in mitral stenosis,[25-29] in Eisenmenger's complex,[19, 30-32] in patent ductus arteriosus,[7, 8, 10-12, 14] and in idiopathic pulmonary hypertension.[23, 33, 34] These reports show that there are characteristic and constant changes in the pulmonary arteries and arterioles associated with severe pulmonary hypertension that are independent of associated congenital or acquired cardiac lesions.

The purpose of the present communication is to describe the clinical and histologic features characteristic of severe pulmonary hypertension and to define hypertensive pulmonary vascular disease as a distinct clinicopathologic entity, which may be regarded as analogous to malignant hypertension in the systemic circulation.

The clinical and pathologic features of hypertensive pulmonary vascular disease are illustrated by reports of 6 patients with different forms of acquired and congenital heart disease complicated by severe pulmonary hypertension. Although only 1 example is given of various cardiac anomalies complicated by a great increase in pulmonary vascular resistance, it must be emphasized that hypertensive pulmonary vascular disease is not a rarity. During the last 3 years this condition has been diagnosed in 10 patients with atrial septal defect, 4 with ventricular septal defect, 14 with Eisenmenger's complex, 12 with patent ductus arteriosus, 3 with idiopathic pulmonary hypertension, and numerous patients with mitral stenosis at the Regional Cardiovascular Centre, Sheffield, under the care of Dr. J. W. Brown.

REPORT OF CASES

Case 1. A married woman, aged 21 years, was admitted as an emergency with hemoptysis. She had

This study was made during the tenure by Dr. Heath of a Leverhulme Research Scholarship of the Royal College of Physicians of London.

From the Regional Cardiovascular Centre, City General Hospital, and the University Department of Medicine, Royal Hospital, Sheffield, England.

been short of breath on exertion since infancy and had suffered from coughs and colds every winter. Her parents noticed that her lips were blue when she was breathless, and for this reason took her at the age of 5 years for examination when, on the basis of a loud precordial systolic murmur, a ventricular septal defect was diagnosed. From the age of 6 she had recurrent nose bleeding and her breathlessness on exertion became worse but she was not cyanosed other than on exertion. At the age of 20 years she coughed up a little bright red blood and after 5 weeks of repeated small hemoptyses suddenly coughed up a pint of blood. A year later she had further hemoptyses that continued until 5 days before her admission, when she complained of a bubbling sensation in her chest and coughed up another pint of blood. Three days after admission she had a further profuse hemoptysis and died.

On admission, she was a tall, thin girl with pallor of the skin and mucous membranes. There were no petechiae. The fingers were long and tapering but were not clubbed. There was no cyanosis at rest, but on slight exertion her lips became blue. The radial pulse was regular at 120/min. and of poor volume. The blood pressure in the arms was 120/80 mm. Hg. The apex beat was palpable in the sixth left intercostal space just beyond the midclavicular line, and the character of the cardiac impulse indicated right ventricular hypertrophy. The second heart sound was palpable in the pulmonary area. A loud systolic murmur was present over the whole precordium but was of maximum intensity in the fourth left intercostal space 2 inches to the left of the sternum. The second sound in the pulmonary area was abnormally loud and just split. The electrocardiogram showed sinus rhythm, clockwise rotation of the heart, and a ventricular pattern of right ventricular hypertrophy (fig. 1). On radiologic examination there was slight over-all cardiac enlargement in the posteroanterior position and evidence of right ventricular hypertrophy in the left anterior oblique view. The pulmonary artery and its main branches were dilated and abnormally pulsatile but the degree of pulsation did not amount to a "hilar dance." There was no evidence of pulmonary tuberculosis (fig. 2). The hemoglobin was 10.2 Gm./100 ml. No tubercle bacilli were found in the sputum. Clinically, the diagnosis was considered to be congenital heart disease with pulmonary hypertension, and in view of the loud systolic murmur there was thought to be an underlying ventricular septal defect.

At autopsy, the heart was enlarged, mainly due to hypertrophy of the right ventricle. A muscular defect in the ventricular septum, 2 cm. in diameter, was found in the region of the apex. The pulmonary artery was dilated to twice its normal diameter and flecks of atheroma were present in the extrapulmonary portions.

On histologic examination, there was no evidence of medial necrosis of the elastic pulmonary

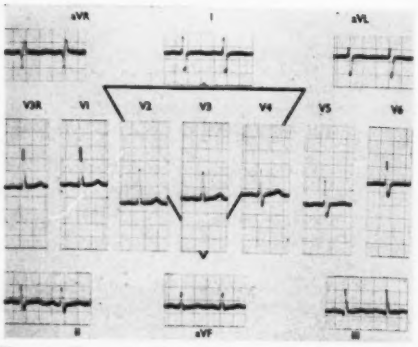


FIG. 1. Case 1. Ventricular septal defect with severe pulmonary hypertension. Electrocardiogram showing ventricular patterns of right ventricular hypertrophy and clockwise rotation of heart.

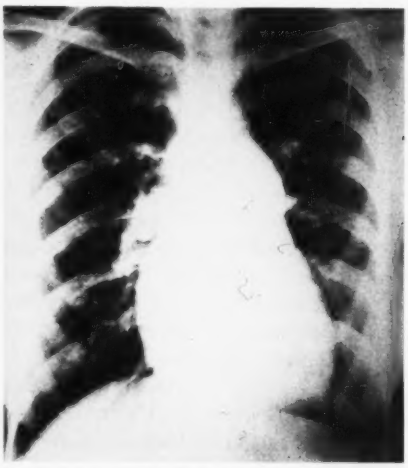


FIG. 2. Case 1. Ventricular septal defect with severe pulmonary hypertension. The teleradiogram shows slight cardiac enlargement with prominence of the pulmonary arteries and its main branches. The peripheral lung fields are clear.

arteries. Although atheroma had been noted in the extrapulmonary arteries, it was not seen in the intrapulmonary portions. The muscular pulmonary arteries (100 to 1000 μ) showed severe and widespread changes, and it was impossible to find a normal muscular pulmonary artery (figs. 12, 19, 20, and 22). The adventitia was thick and fibrous and was infiltrated in many cases by thin wisps of elastic tissue that had split away from the grossly thickened external elastic lamina. The media was hypertrophied with an abnormally thick layer of densely staining, circularly arranged smooth muscle cells peripheral to the internal elastic lamina. This lamina was very thick and there were fine wisps

of elastic tissue spreading into the media. The majority of the muscular arteries were occluded by young fibrous tissue or fibroelastic tissue that had recanalized in many (fig. 22). Some arteries showed medial aplasia, the external and internal membranes fusing into a single lamina between proliferated intimal tissue and adventitia (fig. 20). In some vessels the media was absent for as much as 40 per cent of the circumference, particularly in the region where the bronchioles opened into the infundibulum. At this site, certain of the muscular pulmonary arteries communicated with vessels whose diameter was greater than that of the parent artery. These vessels, which were lined by fibroelastic tissue and filled with blood, were at first thought to be aneurysmal sacs, but on examination of serial sections these sacs were found to be grossly dilated branches of the parent vessel (fig. 19). The arterioles (less than 100 μ in diameter) had a thick adventitia and a definite media bounded by distinct internal and external elastic membranes. The veins showed crescents of sclerotic tissue, partially occluding the lumen.

Case 2. An unmarried man, aged 24 years, was admitted for investigation of congenital heart disease. He had been breathless on exertion since the age of 10 years, and there was a progressive increase in its severity from the age of 18 years until his death at the age of 24. From the time of adolescence, blueness of the lips had been noticed in cold weather, and this was worse on exertion. Hemoptyses occurred at the age of 7 years, and, when an unproductive cough and breathlessness on exertion later developed, he was suspected of having tuberculosis. He had further hemoptyses at the age of 21 and 1 month before his death.

On examination, he had clinical evidence of pulmonary hypertension, judged from giant "a" waves in the jugular venous pulse, a palpable second heart sound in the pulmonary area, a systolic lift over the right ventricular outflow tract, a right ventricular heave, and a loud split second pulmonary sound. Slight central cyanosis and early clubbing of the fingers were noted. The blood pressure in the arms was 110/60 mm. Hg. There were no heart murmurs. The electrocardiogram showed sinus rhythm, clockwise rotation of a vertical heart, and a ventricular pattern of right ventricular hypertrophy. On radiologic examination there were slight over-all cardiac enlargement in the posteroanterior position and evidence of right ventricular hypertrophy in the left anterior oblique view. The pulmonary artery and its main branches were dilated and abnormally pulsatile but the degree of pulsation did not amount to a "hilar dance." There was no evidence of pulmonary tuberculosis (fig. 3). The hemoglobin was 19.5 Gm./100 ml. Angiocardiography showed early filling of the ascending aorta and pulmonary artery from the right ventricle, indicating that there was an overriding aorta. Cardiac catheterization demonstrated a pulmonary-

FIG. 3. Case 2. Eisenmenger's complex. The teleradiogram shows slight cardiac enlargement and increased prominence of the pulmonary artery.

artery mean blood pressure of 90 mm. Hg, and blood samples taken from the right chambers of the heart showed no evidence of a shunt of saturated blood from the left side of the heart. The diagnosis was considered to be Eisenmenger's complex.

At autopsy, the heart was enlarged, mainly due to hypertrophy of the right ventricle. The thickness of the right ventricular wall was 12 mm. and that of the left, 8 mm. There was an overriding aorta and a membranous ventricular septal defect that was concealed behind a much hypertrophied crista supraventricularis. There were flecks of atheroma on the pulmonary artery.

On histologic examination, atheroma was noted in the elastic intrapulmonary arteries. The muscular pulmonary arteries (100 to 1000 μ in diameter) showed widespread severe changes, consisting of medial hypertrophy and obliteration of the lumen by fibrous tissue that had proliferated from the intima (fig. 10). The elastic laminae were thick and wavy in appearance. The pulmonary arterioles (less than 100 μ in diameter) showed similar changes in the media and intima (fig. 18). The small pulmonary veins appeared to be normal, with no evidence of thrombosis or sclerosis.

Case 3. A married woman, aged 58 years, complained of breathlessness on exertion and had frequent coughs and colds. She had noted occasional cyanosis. On examination she had the classical signs of pulmonary hypertension, such as giant "a" waves in the jugular venous pulse, a systolic lift over the right ventricular outflow tract, a palpable second sound in the pulmonary area, and an abnormally loud pulmonary element of the second heart sound on auscultation. She had moderate central cyanosis

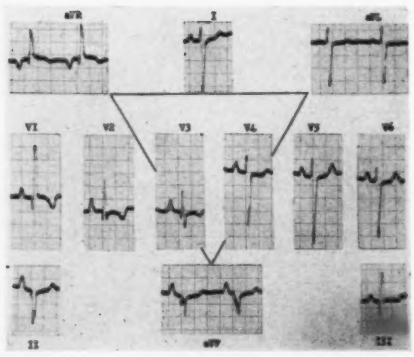


FIG. 4. Case 3. Patent ductus arteriosus with severe pulmonary hypertension. Electrocardiogram showing ventricular patterns of right ventricular hypertrophy and clockwise rotation.

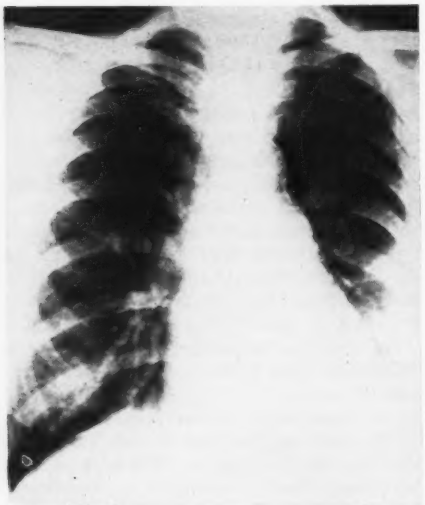


FIG. 5. Case 3. Patent ductus arteriosus with severe pulmonary hypertension. The teleradiogram shows slight cardiac enlargement with increased prominence of the pulmonary artery and its main branches.

and clubbing of the fingers. There were no cardiac murmurs but there was a triple rhythm at the lower end of the sternum. The blood pressure in the arms was 160/105 mm. Hg. The electrocardiogram showed clockwise rotation and the ventricular pattern of right ventricular hypertrophy (fig. 4). Radiologic examination revealed slight over-all cardiac enlargement in the posteroanterior position and evidence of right ventricular hypertrophy in the left anterior oblique view. The pulmonary artery and its main branches were dilated and abnormally pulsatile but the degree of pulsation did not amount to a "hilar dance" (fig. 5). The hemoglobin was 25.0 Gm per cent. Angiocardiography and cardiac catheterization were not performed. The clinical diagnosis was restricted to cyanotic congenital heart disease with pulmonary hypertension.

At autopsy, the heart weighed 460 Gm. and the right ventricle was dilated and hypertrophied. The wall of the right ventricle was 16 mm. thick and that of the left ventricle 18 mm. The main pulmonary artery was dilated, and the abnormally dilated and thick-walled intrapulmonary arteries stood out more clearly than usual on the cut surface of the lung. The left pulmonary artery was blocked by antemortem thrombus, and old portions of antemortem thrombus were found in its branches, especially those to the lower lobe, which was infarcted and showed pleurisy of several days' duration. There was a large patent ductus arteriosus leading from the descending aorta into the pulmonary artery at its bifurcation. This vessel was 1 cm. long and about 2 cm. in diameter. Its site of origin in the descending aorta showed that it was a patent ductus arteriosus rather than an aortopulmonary septal defect. There was widespread atheroma of both extrapulmonary and the elastic intrapulmonary arteries. The diagnosis appeared to be patent ductus arteriosus with severe pulmonary hypertension.

On histologic examination there was gross atheromatous change in the elastic pulmonary arteries (more than 1000 μ in diameter); in some of these vessels the atheromatous material was 4 times the thickness of the media. At the junction of the media and intima the elastic fibers were ruptured in many places, but the more peripheral fibers were normal. The adventitia was normal.

The muscular pulmonary arteries (100 to 1000 μ in diameter) showed a proliferation of fibroelastic tissue in the intima that occluded the lumen in many vessels, some of which were recanalized. The media of the muscular pulmonary arteries was hypertrophied (fig. 11). Both elastic membranes were well defined and, although the internal elastic membrane was thicker than normal, it was not split. The adventitia was normal. The arterioles (less than 100 μ in diameter) showed similar changes in the media and intima as the muscular pulmonary arteries (fig. 17). In some, proliferated intimal tissue had completely disorganized the structure of the vessels. The pulmonary veins were normal, and there was no evidence of thrombosis in the small veins.

Case 4. A married woman, aged 41 years, was well until 10 years before admission when she developed progressive dyspnea on exertion. She had always had a "high color" but had never noticed that she was cyanosed until she became breathless; then as dyspnea increased, cyanosis became marked. On admission, her exercise tolerance was extremely limited. Four months previously she had noticed swelling of the ankles, palpitation, and occasional

stabbing pains in the left side of her chest. There was no history of cough or hemoptysis.

On examination, there was marked central cyanosis, polycythemia and clubbing of the fingers. The jugular venous pulse showed no giant "a" waves but there was a right ventricular heave, a systolic lift over the right ventricular outflow tract, and a palpable second sound in the pulmonary area, which was loud and split on auscultation. There were no cardiac murmurs. The apex beat was in the anterior axillary line in the fifth left intercostal space, and the character of the cardiac impulse suggested right ventricular hypertrophy. There was sinus rhythm, at 100/min., with occasional extrasystoles. The blood pressure in the arms was 130/80 mm. Hg. The femoral pulses were palpable. The electrocardiogram showed qR patterns in leads V_1 and V_2 which were evidence of marked right ventricular hypertrophy. The teleradiogram showed gross over-all cardiac enlargement, particularly to the left, with marked fullness of the pulmonary conus. Oblique views suggested enlargement of both ventricles and of the right atrium. The main branches of the pulmonary artery were prominent and abnormally pulsatile but the peripheral vessels were not enlarged. Angiocardiography demonstrated a large right atrium from which dye flowed abnormally through an atrial septal defect into a large left atrium. The ascending aorta filled almost immediately after the left atrium. At cardiac catheterization the mean blood pressure was 70 mm. Hg in the pulmonary artery and 10 mm. Hg in the right atrium; the oxygen saturation of blood samples rose from 40 per cent in the superior vena cava to 61 per cent in the right atrium. These results were compatible with a diagnosis of an atrial septal defect complicated by severe pulmonary hypertension.

This patient is still alive, but the small pulmonary vessels of another case of atrial septal defect with pulmonary hypertension were studied at autopsy. The pulmonary arterioles (less than 100 μ in diameter) showed slight intimal sclerosis and a definite media of smooth muscle cells lying between internal and external elastic laminae. The adventitia was fibrous. The elastic pulmonary arteries (more than 1000 μ in diameter) showed atheromatous deposits in the intima, but there was no medial necrosis. The media of the muscular pulmonary arteries (100–1000 μ in diameter) was hypertrophied.

Case 5. A married woman, aged 41, was admitted for mitral valvotomy. She had suffered from progressive dyspnea for 6 years and had been restricted to bed for 2 years with this symptom. She had had an unproductive cough for several years and hemoptysis for the few weeks prior to her admission to hospital. She also had an anginal type of pain.

On examination, there were giant "a" waves in the jugular venous pulse, a systolic lift over the right ventricular outflow tract, a right ventricular heave, and a palpable second sound in the pulmonary

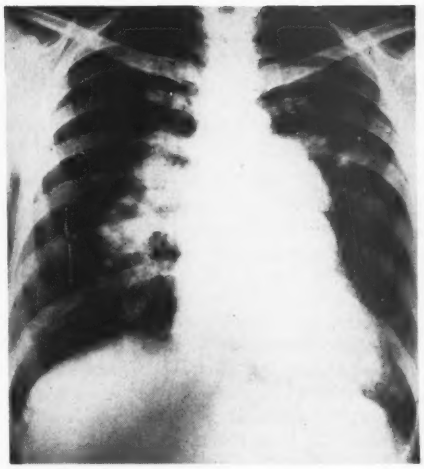


FIG. 6. Case 5. Mitral stenosis with severe pulmonary hypertension. The teleradiogram shows slight cardiac enlargement and extreme prominence of the pulmonary artery and its main branches. The peripheral lung fields are abnormally clear.

area, which was loud and split on auscultation. There was no central cyanosis. The pulse was regular at 72/min. The blood pressure in the arms was 130/90 mm. Hg. On radiologic examination there was extreme dilatation of the pulmonary artery and its main branches, with clear peripheral lung fields (fig. 6). A pulmonary artery mean blood pressure of 108 mm. Hg was recorded at cardiac catheterization. Mitral valvotomy was performed successfully and produced symptomatic relief from dyspnea. A biopsy of the lung was obtained at this time. Three years after operation she was admitted as an emergency with a systemic blood pressure of 220/120 mm. Hg and a pontine hemorrhage, from which she died.

At autopsy, the heart showed left ventricular and right ventricular hypertrophy and weighed 500 Gm. The mitral valve was stenosed and admitted only 1 finger. The aortic valve was normal. There was slight pulmonary atheroma, and the pulmonary artery was dilated.

On histologic examination, the appearances in the lung biopsy were identical with those found at autopsy 3 years later. The pulmonary arterioles (less than 100 μ in diameter) were grossly abnormal. There was a definite muscular media lying between internal and external elastic laminae. The adventitia was thick and fibrous, and intimal fibrous proliferation had occluded most of these vessels. Recanalization of this proliferated fibroelastic tissue had occurred in many vessels. In some the structure of the pulmonary arterioles had been completely lost, and the vessels appeared like scars of fibrous tissue. The muscular pulmonary arteries (100 to 1000 μ

in diameter) had medial hypertrophy and the adventitia was thick and fibrous. There was intimal sclerosis. The elastic intrapulmonary arteries (over 1000 μ in diameter) showed intimal deposits of atheroma, but there was no medial necrosis. The veins were normal apart from the normal age change of intimal sclerosis.

Case 6. A girl, aged 12 years, was admitted in congestive cardiac failure. At the age of 5 she became breathless on exertion and developed central cyanosis. On examination she showed cyanosis and clubbing of the fingers and was in gross congestive heart failure with ankle edema, a greatly enlarged liver, ascites, and raised jugular venous pressure. The pulse was regular at 68/min. The blood pressure was 130/88 mm. Hg. There were giant "a" waves in the jugular venous pulse, a systolic lift over the right ventricular outflow tract, a palpable second sound in the pulmonary area, and a parasternal heave. There was a thrill and a harsh systolic murmur in the mitral area. In the pulmonary area were heard a loud second sound and a Graham Steell murmur. An electrocardiogram showed the ventricular pattern of right ventricular hypertrophy, right axis deviation, and peaked P waves. A teleradiogram showed gross cardiac enlargement with marked prominence of the main pulmonary artery and clear peripheral lung fields (fig. 7). Abnormal pulsation of the pulmonary arteries was seen that did not amount to "hilar dance." The left atrium was of normal size but the right ventricle was hypertrophied.

Response to mersalyl therapy was disappointing, and the patient died suddenly.

On examination of the heart there was gross right ventricular hypertrophy, the thickness of the free wall of the right ventricle being 10 mm. The pulmonary arteries were dilated and atheromatous. The right atrium was much dilated. When the lung was cut, the small pulmonary blood vessels stood out more clearly than usual. There were no septal defects, no valvular lesions, and no transposition of the great vessels. The ductus arteriosus was occluded.

On histologic examination of the pulmonary arterioles (less than 100 μ in diameter) there were distinct muscular media, with internal and external elastic laminae, and such severe intimal fibrosis that most of these vessels were almost totally occluded. The adventitia was thick and fibrous.

The media of the muscular pulmonary arteries (100 to 1000 μ in diameter) was grossly abnormal. Some sections showed medial necrosis, some medial hypertrophy, and others medial hypoplasia and aplasia (fig. 21). Over the areas of medial hypoplasia there was marked intimal proliferation. Tubercles of fibrous tissue were scattered throughout the lung and were seen mainly in close association with pulmonary blood vessels, the appearances being similar to that of a healing periarteritis nodosa. The elastic intrapulmonary arteries (more than 1000 μ in diameter) were normal apart from atheromatous deposits on the intima. The pulmonary veins were normal. The lung as a whole presented a strikingly avascular appearance.

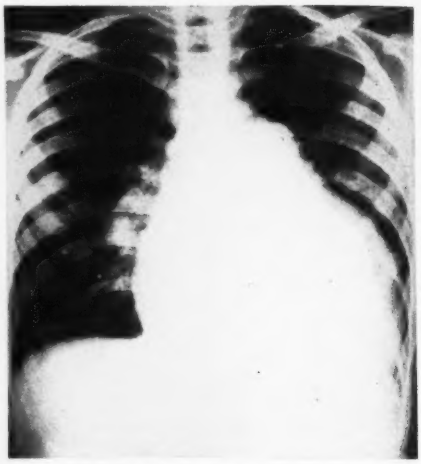


FIG. 7. Case 6. Idiopathic pulmonary hypertension. The teleradiogram shows marked cardiac enlargement with increased prominence of the pulmonary artery and its main branches. The peripheral lung fields are abnormally clear.

DISCUSSION

Symptomatology

Symptoms that commonly occur in patients with hypertensive pulmonary vascular disease are breathlessness on exertion, frequent coughs and colds, chest pain of anginal type, blueness of the lips and nails, and abdominal distention and ankle swelling due to congestive cardiac failure. Hemoptysis, hoarseness, syncopal attacks, palpitation, and jaundice also occur less commonly. Although none of these symptoms is pathognomonic, together they produce a symptom complex characteristic of pulmonary hypertension, which occurred in a complete or incomplete form in all the present cases and in the majority of patients with severe pulmonary arterial hypertension seen at the Cardiovascular Unit, Sheffield.

Exertional dyspnea has usually been reported as the dominant symptom in patients with idiopathic pulmonary hypertension,[21-23, 34-39] with patent ductus arteriosus and severe pul-

monary hypertension,[8-12, 14, 39] with Eisenmenger's complex,[19, 40, 41] with atrial septal defects with severe pulmonary hypertension,[39] and in a patient with a muscular ventricular septal defect with severe pulmonary hypertension.[20] From a histologic study of the pulmonary arteries in a child of 11 months with Eisenmenger's complex, Edwards[42] postulated that the onset of breathlessness coincided with the development of occlusive changes in the small pulmonary blood vessels.

Chest pain is a common symptom in patients with hypertensive pulmonary vascular disease. It occurred in cases 4 and 5 of the present series and has also been reported in patients with idiopathic pulmonary hypertension,[21, 22, 33, 34] and in patients with patent ductus arteriosus and pulmonary hypertension.[12] Dresdale, Schultz, and Michtom[21] thought that the chest pain associated with pulmonary hypertension so resembled angina pectoris that it must be due to the high right ventricular blood pressures obstructing the coronary blood flow to the hypertrophied right ventricle. They emphasized that there was no associated coronary artery disease in these patients. However, Viar and Harrison[43] noted that nitroglycerin had no effect on this chest pain and suggested that pulmonary hypertension caused it by distending the main pulmonary arteries. They believed that pain occurred only in a minority of patients with pulmonary hypertension and that, the greater the degree of distention of the main pulmonary arteries, the more severe was the pain. They thought that the location, radiation, quality, and intensity of the pain associated with pulmonary hypertension was identical with that of coronary artery disease but believed that it could usually be differentiated from angina pectoris by the associated clinical, electrocardiographic, and radiologic signs of pulmonary hypertension.

In a male patient aged 26 years suffering from idiopathic pulmonary hypertension, Brinton[28] commented on loss of voice as a striking symptom. On examination there was paralysis of the left vocal cord that was probably due to pressure on the recurrent laryngeal nerve by a grossly dilated pulmonary artery associated with pulmonary hypertension. Hoarseness and aphonia have also been reported in cases of Eisenmenger's complex[44, 45] and is to be expected in patients with severe pulmonary hypertension who have very large pulmonary arteries. Brown, Heath, and Whitaker[19] thought that hoarseness had not occurred in their series of Eisenmenger's complex because none of the patients had extreme dilatation of the pulmonary arteries.

Congestive cardiac failure, which has been described frequently in patients with idiopathic pulmonary hypertension,[34, 39, 46] may be expected in any patient with hypertensive pulmonary vascular disease. Abdominal distention, hepatomegaly, and jaundice often occur with this complication, due to tricuspid incompetence.

Hemoptysis does not occur so commonly as breathlessness, chest pain, and blueness of the lips and nails, but it has been described with idiopathic pulmonary hypertension,[21] with patent ductus arteriosus and severe pulmonary hypertension,[7, 8, 14] with a ventricular septal defect and pulmonary hypertension,[20] and with Eisenmenger's complex.[19] Bond,[41] however, did not mention hemoptysis in his review of 18 cases of Eisenmenger's complex.

Profuse hemoptysis such as occurred in case 1 of the present series is probably arterial in origin, arising from ruptured aneurysmal dilatations of the thin-walled branches of the muscular pulmonary arteries. In patients suffering from mitral stenosis, hemoptysis may arise from dilated pulmonary veins and capillaries, but Wood[47] pointed out many other causes of hemoptysis in such patients. He thought that the development of a high vascular resistance in the pulmonary arterioles, associated with pulmonary hypertension, protected the veins from the raised pulmonary artery blood pressure and led to cessation of bleeding into the lung.

Frequent coughs and colds have been a common feature of patients with severe pulmonary hypertension.[14, 19, 20] Evans[39] believes that cough is a causative agent in the production of structural changes in the small pulmonary blood vessels in patients with abnormally high pulmonary artery blood pressure.

Syncopal attacks have been described in

patients suffering from hypertensive pulmonary vascular disease. They have occurred especially in patients with idiopathic pulmonary hypertension[22, 34] and were sometimes associated with palpitation.[21, 23]

Blueness of the lips, which is a common symptom in hypertensive pulmonary vascular disease, is considered with the clinical signs.

Signs

The present cases illustrate that the clinical picture of hypertensive pulmonary vascular disease is dominated by signs of pulmonary hypertension that Bedford[48] in a recent review described as a parasternal heave, a systolic lift over the right ventricular outflow tract, a palpable second sound in the pulmonary area, which is loud and split on auscultation, and a Graham Steell murmur. Although there is usually clinical evidence of right ventricular hypertrophy and often accentuation of the "a" waves in the jugular venous pulse[22] in patients with severe pulmonary hypertension, other authors[33-39] have not commented particularly on these signs but have stressed the presence of a loud second sound in the pulmonary area. Cutler and his colleagues[24] were impressed by the diagnostic importance of the accentuated second sound in the pulmonary area, but since loud single pulmonary second sounds are sometimes heard in patients with Fallot's tetralogy, who also have clinical signs of right ventricular hypertrophy, such a loud sound is not conclusively diagnostic of a raised pulmonary artery blood pressure. Often, as noted by Wood,[22] there is a close splitting of the second sound in the pulmonary area in patients with pulmonary hypertension, which distinguishes this sound from the loud second sound occasionally heard in Fallot's tetralogy; but sometimes no splitting can be detected. In our experience with patients with severe pulmonary hypertension,[14, 19, 20, 29, 46] there were always other signs of this complication associated with a loud split second sound in the pulmonary area.

In occasional patients with severe pulmonary hypertension, a sharp sound is heard in the pulmonary area closely following the first heart sound. This pulmonary systolic click occurs simultaneously with, or a brief instant after, the rise in pressure in the pulmonary artery at the time when the wall of the pulmonary artery is being most rapidly expanded, and was described as a sign of pulmonary hypertension by Leatham and Vogelpoel.[49]

Central cyanosis frequently occurs in patients with hypertensive pulmonary vascular disease. It is usually due to an abnormally high blood pressure in the right side of the heart that causes deoxygenated blood to flow directly into the systemic circulation through an associated congenital anomaly such as a ventricular septal defect,[20] an atrial septal defect, a patent ductus arteriosus,[8-12, 14] or an overriding aorta in Eisenmenger's complex.[19, 30, 41, 9] When cyanosis occurs in patients with hypertensive pulmonary vascular disease without a cardiac defect that allows venous blood to bypass the lungs, it is usually due to peripheral stasis, but it is sometimes caused by imperfect aeration of blood in the lungs. Cyanosis was described in patients with idiopathic pulmonary hypertension by Gilmour and Evans,[33] and Branwood,[34] but in similar patients[21, 23, 24] the oxygen saturation of arterial blood samples was found to be normal until the terminal stage of congestive heart failure. While it is usual for arterial blood oxygen unsaturation to occur only with the development of congestive heart failure in patients with idiopathic pulmonary hypertension, Ordway[51] described a patient who had unsaturated blood even during the inhalation of 100 per cent oxygen. This unsaturation must have been due to imperfect aeration of the pulmonary arterial blood, which may have been the result of the anatomic changes in the small pulmonary blood vessels caused by pulmonary hypertension.

Clubbing of the fingers occurred in all 7 patients with severe pulmonary hypertension described by Cutler and his associates[24] and was probably due to the duration and degree of arterial oxygen unsaturation.

Hypertensive pulmonary vascular disease frequently causes congestive cardiac failure. Hepatic enlargement and ascites, due to the development of tricuspid incompetence, are common terminal features,[21-23, 35-38] and were observed in case 1.

Cardiac murmurs in hypertensive pulmonary vascular disease may be due to either an underlying cardiac anomaly or to pulmonary incompetence. The murmurs classical of a particular congenital anomaly usually change their character or diminish to the point of total disappearance when there is associated pulmonary hypertension. Of 8 patients with patent ductus arteriosus and severe pulmonary hypertension reported by Whitaker, Heath, and Brown,[14] only 1 had a Gibson murmur, while 2 had only a basal systolic murmur, 1 had only a basal diastolic murmur, 1 had a basal systolic murmur and diastolic murmur, and 3 had no murmurs at all. Cases of mitral stenosis with severe pulmonary hypertension have also been seen in which the characteristic apical diastolic murmur was absent.

Hypertensive pulmonary vascular disease is much commoner in female patients. All 3 cases of Branwood,[34] all 7 cases of Cutler and his associates,[24] the case of Evans,[39] 2 of the 3 cases of Cosh,[11] 5 of the 8 cases of Hultgren and his colleagues,[12] 7 of the 8 cases reported by Whitaker, Heath, and Brown,[14] 4 of 7 cases of Brown, Heath, and Whitaker,[19] and the patient of Heath, Brown, and Whitaker[20] were female. The higher frequency of hypertensive pulmonary vascular disease in women is probably explained by the greater incidence in this sex of cardiac anomalies, such as atrial septal defect, patent ductus arteriosus, and mitral stenosis, that predispose to this complication.

Hypertensive pulmonary vascular disease usually develops insidiously, but sudden death is frequent. The patients with idiopathic pulmonary hypertension reported by Gilmour and Evans,[33] Branwood,[34] and Evans[39] all died suddenly. Similarly, the cases of pulmonary hypertension complicating congenital dilatation of the pulmonary artery, patent ductus arteriosus, atrial septal defect, and pulmonary disease reported by Evans[39] all terminated suddenly. The cause of death may be obvious as in case 1 of the present series, who died from a profuse hemoptysis, but often it is obscure.

Laboratory Studies

Patients with hypertensive pulmonary vascular disease consistently show electrocardiographic evidence of associated right ventricular hypertrophy (figs. 1 and 4). The common electrocardiographic pattern is of right ventricular hypertrophy and strain but occasionally there may be a pattern of incomplete right bundle-branch block. Electrocardiograms of this type have been reported in patients with idiopathic pulmonary hypertension,[22, 23, 33-38] with patent ductus arteriosus and severe pulmonary hypertension,[7, 11, 12, 14] with Eisenmenger's complex,[16, 17, 19] with a ventricular septal defect and pulmonary hypertension,[20] and with mitral stenosis and pulmonary hypertension.[6, 22] Abnormally peaked P waves due to associated right atrial hypertrophy may also occur.[14, 22, 35] Although electrocardiographic patterns of right ventricular hypertrophy are not pathognomonic of pulmonary hypertension, they invariably occur with this condition and are necessary for its diagnosis unless there is also some associated condition causing left ventricular hypertrophy such as systemic hypertension.[19]

On radiologic examination all the patients in the present series showed increased prominence of the pulmonary artery and its main branches, with decreased peripheral pulmonary vascular markings, right ventricular hypertrophy, and right atrial dilatation (figs. 2, 3, 5–7). These signs are characteristic of hypertensive pulmonary vascular disease and occur irrespective of whether this is primary or secondary to some form of congenital or acquired heart disease. In the latter cases, however, the appearances may be modified by an underlying cardiac anomaly. They have been reported in patients with idiopathic pulmonary hypertension,[22, 23, 33, 35, 36-38] with patent ductus arteriosus and severe pulmonary hypertension,[14] and with ventricular septal defect and pulmonary hypertension.[20] In addition to the above radiologic signs, Whitaker and Lodge[52] observed horizontal lines at the lung bases, due to lymphatic stasis, in some patients with mitral stenosis and pulmonary hypertension. These latter patients usually have diagnostic enlargement of the left atrium and some also show pulmonary hemosiderosis, which does not occur in other patients with hypertensive pulmonary vascular disease. Patients with a ventricular septal defect or a patent ductus arteriosus

usually have radiologic evidence of left as well as right ventricular hypertrophy; but this sign is of little diagnostic importance, since other patients with pure right ventricular hypertrophy occasionally appear to have associated left ventricular hypertrophy.[16] Increased pulsation of the pulmonary arteries is usual but does not amount to a "hilar dance".[14, 19]

Angiocardiography is most informative in cyanosed patients with hypertensive pulmonary vascular disease when there is an abnormal shunt of blood from the right to the left side of the heart. In such patients, abnormal flows are visualized and previously unrecognized cardiac defects demonstrated. The importance of angiocardiography as a means of showing the overriding aorta in patients with Eisenmenger's complex was emphasized by Brown and his associates.[19] Cosh[11] and Whitaker and his colleagues[14] described simultaneous filling of the pulmonary arteries and the descending aorta before contrast medium was seen in the ascending aorta in patients with patent ductus arteriosus and severe pulmonary hypertension. Many observers, including the present authors, have demonstrated atrial septal defects by angiocardiography when there has been abnormal flow of blood from right to left atrium. In addition to its diagnostic value in showing abnormal intracardiac shunts, angiocardiography also reveals a pulmonary vascular pattern that is characteristic of hypertensive pulmonary vascular disease. The pulmonary artery and its main divisions are dilated while the branches from the right and left pulmonary arteries show a coppicing effect. Sometimes the dilatation is slight as in the series of patients with Eisenmenger's complex reported by Brown, Heath, and Whitaker,[19] but occasionally it is extreme as in cases of Eisenmenger's complex reviewed by Campbell.[53] By venous angiocardiography, Goodwin and his associates[54] showed in patients with mitral stenosis and pulmonary hypertension that the arteries at the bases of the lungs were narrow and irregular in contrast to the enlargement of the main branches of the pulmonary artery. They thought that the severity of the changes bore a direct relation to the height of the pulmonary arterial pressure. Davies and his colleagues[55] also found that the narrowing affected arteries with a predominantly muscular coat while the large branches, which have relatively little muscle in their walls, were dilated. These latter authors thought that the severity of pulmonary hypertension could be gaged from arterial changes seen on a plain radiograph; they claimed that examination of a technically satisfactory radiograph of the chest was the best clinical guide to the level of the pulmonary arterial pressure.

The flow through the pulmonary blood vessels in patients with hypertensive pulmonary vascular disease is abnormally slow; at angiocardiography contrast medium lingers in the pulmonary arterial tree and it is unusual to find any in the left side of the heart within 8 seconds of injection.

Pulmonary artery blood pressures can be recorded directly by cardiac catheterization; by this means pulmonary hypertension of the order of systemic arterial blood pressures can be demonstrated in all patients with hypertensive pulmonary vascular disease. This investigation is particularly useful in differentiating patients with Fallot's tetralogy with loud or even palpable second sounds in the pulmonary area, from patients with hypertensive pulmonary vascular disease. Frequently underlying congenital anomalies, such as atrial or ventricular septal defects and patent ductus arteriosus, are recognized when the cardiac catheter passes through the defect. The abnormally high pulmonary artery blood pressure in patients with hypertensive pulmonary vascular disease often makes it difficult to record "arterial wedge" pressures, but when these have been satisfactorily recorded they have been normal, except in patients with mitral stenosis. Since patients with septal defects complicated by severe pulmonary hypertension usually develop a shunt from the right to the left side of the heart, examination of the oxygen saturation of blood samples is often of little diagnostic importance. However, when the flow of blood is not completely from right to left, the blood oxygen saturations provide some evidence of the intracardiac defect as in the case of Eisenmenger's complex described by Bing and his colleagues.[15] The oxygen

saturations of mixed venous blood may be normal but are sometimes low, indicating a small cardiac output that is reflected in the marked peripheral cyanosis commonly found with hypertensive pulmonary vascular disease.

In patients with idiopathic pulmonary hypertension, or mitral stenosis with pulmonary hypertension, the arterial blood oxygen saturation is usually normal, but may be slightly reduced when there is cardiac failure. The degree of arterial blood oxygen unsaturation in patients with septal defects varies with the degree of reversal of flow. Cosh[11] and Whitaker and his associates[14] noted that cyanosis was most marked in the lower extremities in patients with patent ductus arteriosus and pulmonary hypertension. Most patients with oxygen unsaturation of arterial blood become polycythemic; the hemoglobin levels may rise so high as to mimic polycythemia rubra vera.[14] Respiratory function has not usually been studied in patients with hypertensive pulmonary vascular disease but Howarth and her colleagues[35] reported a patient with idiopathic pulmonary hypertension with a vital capacity of 2.3 L. In one patient with a ventricular septal defect and pulmonary hypertension and in another with idiopathic pulmonary hypertension[46] investigated in this unit, vital capacity, maximum breathing capacity, and helium-mixing curves were normal.

Pulmonary Vascular Histology

The small pulmonary blood vessels in the patients with severe pulmonary arterial hypertension described here showed a distinct muscular media in the pulmonary arterioles (less than 100 μ in diameter) (figs. 14–18) and medial hypertrophy in the muscular pulmonary arteries (between 100 and 1000 μ in diameter). The thickness of the media in these latter vessels exceeded 15 per cent of the external diameter (figs. 9–12). These appearances are pathognomonic abnormalities that have been constantly observed in patients with severe pulmonary hypertension. They have already been described as histologic signs of severe pulmonary hypertension in mitral stenosis,[29] in patent ductus arteriosus,[14] in Eisenmenger's complex,[19] in a patient with a muscular ventricular septal defect with severe pulmonary hypertension,[20] and in others with idiopathic pulmonary hypertension.[46] Although Cudkowicz and Armstrong[56] believe that it is impossible to distinguish between pulmonary and bronchial arterioles, there is usually no difficulty in differentiating the abnormal pulmonary vessels associated with pulmonary hypertension from branches of the bronchial arteries. However, in diseases associated with the development of an extensive bronchial collateral circulation to the lungs, such as bronchiectasis, Fallot's tetralogy, and pulmonary atresia, care must be taken in assessing the significance of a distinct muscular media in pulmonary blood vessels below 100 μ in diameter. The earliest sign of pulmonary arterial hypertension in the pulmonary vasculature is the appearance of a muscular media in the pulmonary arterioles, which normally show no distinct media in human lung (fig. 13). This abnormal media has been found consistently in the pulmonary arterioles of all patients with resting pulmonary artery mean blood pressures exceeding 50 mm. Hg and has often been the only abnormal histologic sign when the pulmonary artery mean blood pressures have been less than 90 mm. Hg (figs. 14–16). Heath and Whitaker,[29, 57] have stressed the importance of a distinct media in the pulmonary arterioles and have pointed out that unless this is recognized as an abnormal sign, pulmonary vessels may sometimes be regarded as normal in patients with moderate pulmonary hypertension.

In patients such as those in the present series with pulmonary artery blood pressures of the order of the systemic blood pressure, there are usually gross changes in addition to an abnormal media in the pulmonary arterioles and medial hypertrophy in the muscular pulmonary arteries. Frequently with severe pulmonary hypertension there is abnormal proliferation of intimal fibrous tissue with partial or complete occlusion of the lumen (figs. 10–12, 17, 18, and 22), adventitial fibrosis (figs. 17 and 22), arterial and arteriolar medial necrosis (fig. 21), and aneurysmal dilatation of thin-walled branches of the muscular pulmonary arteries (fig. 19); these are the definitive histo-

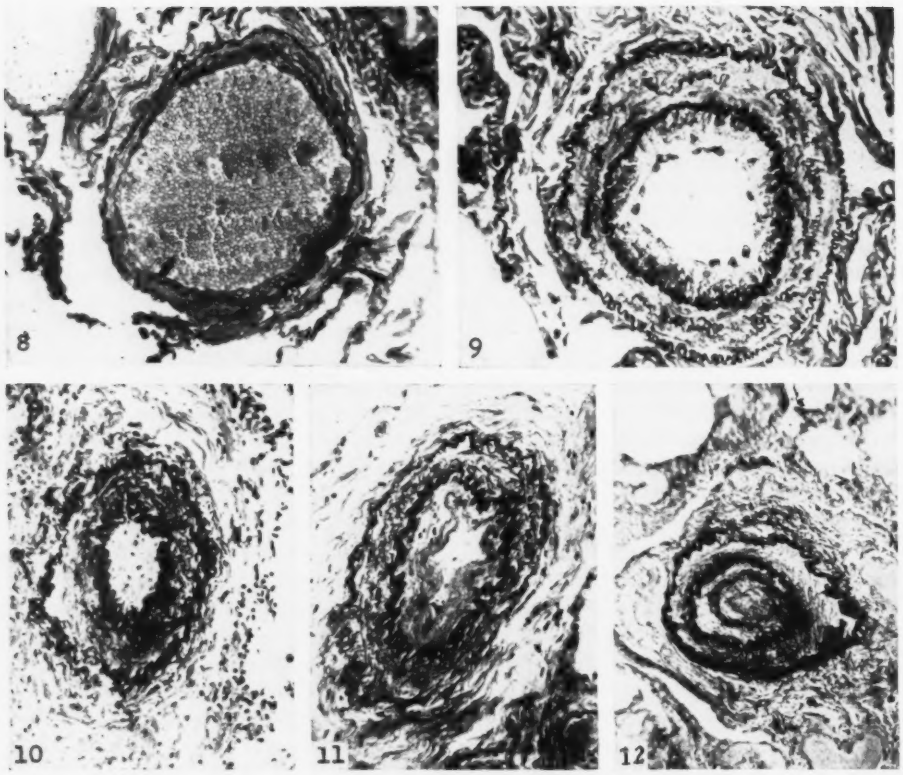


FIG. 8. Transverse section of a muscular pulmonary artery (diameter 300 μ) from a case of mitral stenosis with mild pulmonary hypertension. Mean pulmonary artery blood pressure = 33 mm. Hg. There is a thin media bounded by thin, unsplit elastic membranes. There is minimal subintimal proliferation of fibrous tissue and the adventitia is thin. The appearance of the vessel is normal. Verhoeff-Van Gieson stains were used in all microscopic sections illustrated.

FIG. 9. Transverse section of a muscular pulmonary artery (diameter 160 μ) from a case of mitral stenosis with severe pulmonary hypertension. Mean pulmonary artery blood pressure = 74 mm. Hg. There is a hypertrophied media, and the elastic membranes are thick. Subintimal proliferation of fibrous tissue has occurred.

FIG. 10. Case 2. Eisenmenger's complex. Muscular pulmonary artery (diameter 270 μ). In figures 10–12 there is medial hypertrophy, thickening of the internal and external elastic laminae and adventitial fibrosis. There is also partial or complete occlusion of the lumen by intimal proliferation of fibrous tissue.

FIG. 11. Case 3. Patent ductus arteriosus with severe pulmonary hypertension. Muscular pulmonary artery (diameter 300 μ).

FIG. 12. Case 1. Muscular ventricular septal defect with severe pulmonary hypertension. Muscular pulmonary artery (diameter 145 μ).

logic features of hypertensive pulmonary vascular disease.

Many previous accounts of histologic lesions in the pulmonary vessels are difficult to assess, since some observers have failed to state the type of pulmonary vessel they were describing, making it impossible to decide whether the presence of a media was significant or not. Others have used vague pathologic terms such as "pulmonary arteriosclerosis" from which it is impossible to decide whether the authors are referring to the normal age change of intimal sclerosis, described by Brenner[58] and Heath and Whitaker[29, 57] (fig. 8), or to the coarse intimal

fibrosis with admixed elastic fibrils that is characteristic of hypertensive pulmonary vascular disease (figs. 9–12, 17, and 18). There are, however, some clear accounts of pulmonary vascular lesions. Arterial necrosis has been recognized in idiopathic pulmonary hypertension,[59, 60] in mitral stenosis,[27, 59, 61] in patent ductus arteriosus with severe pulmonary hypertension,[12] in Eisenmenger's complex,[32, 62] and by McKeown[63] in cases of unknown etiology. The importance of a distinct media in the pulmonary arterioles was realized by Henry[62]

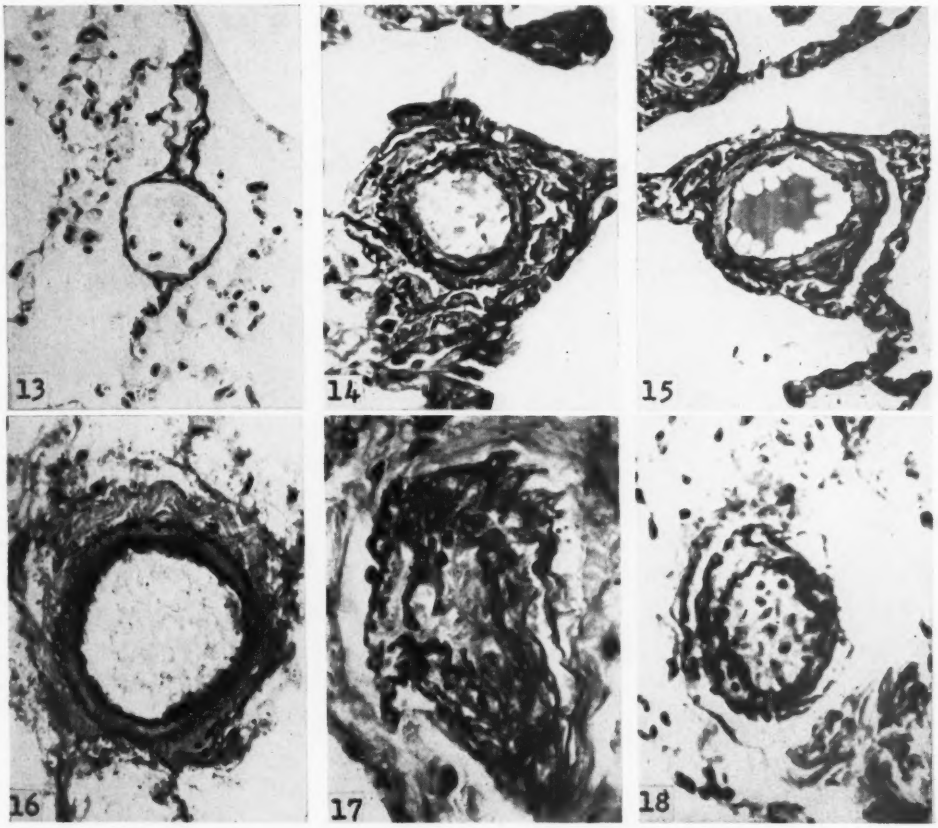


FIG. 13. Transverse section of a normal pulmonary arteriole (diameter $<100\ \mu$). There is a single elastic lamina lying between the endothelium and a thin adventitia. There is no subintimal proliferation of fibrous tissue.

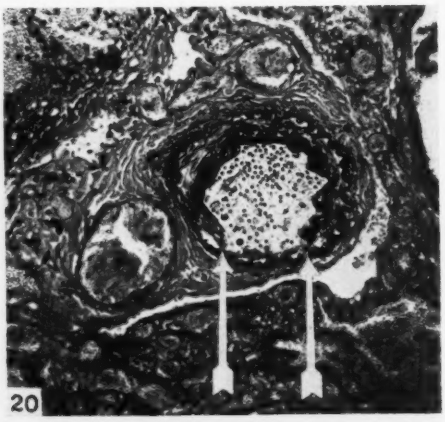
FIG. 14. Mitral stenosis. Mean pulmonary artery blood pressure = 74 mm. Hg. Pulmonary arteriole (diameter $55\ \mu$). In figures 14–16 there is a distinct muscular media with internal and external elastic laminae.

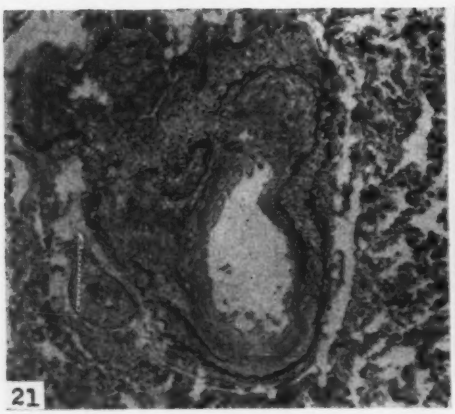
FIG. 15. Patent ductus arteriosus. Mean pulmonary artery blood pressure = 65 mm. Hg. Pulmonary arteriole (diameter $45\ \mu$).

FIG. 16. Idiopathic pulmonary hypertension. Mean pulmonary artery blood pressure = 70 mm. Hg. Pulmonary arteriole (diameter $80\ \mu$).

FIG. 17. Case 3. Patent ductus arteriosus with severe pulmonary hypertension. Pulmonary arteriole (diameter $70\ \mu$). In figures 17 and 18 there is a distinct muscular media with internal and external elastic laminae, occlusion of the lumen by intimal proliferation of fibrous tissue and adventitial fibrosis.

FIG. 18. Case 2. Eisenmenger's complex. Pulmonary arteriole (diameter $80\ \mu$).





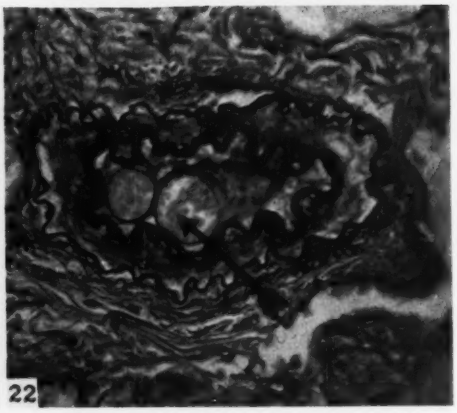


FIG. 19. Transverse section of a muscular pulmonary artery (diameter 210 μ) from case 1, who had a muscular ventricular septal defect and severe pulmonary hypertension. A blood filled sac, indicated by lower arrow, is seen in communication with the artery, indicated by upper arrow. This sac proved on serial section to be a grossly dilated branch of the parent vessel. The external elastic lamina was ruptured opposite the emergence of the dilated branch.

FIG. 20. Case 1. Transverse section of a muscular pulmonary artery (diameter 160 μ). Aplasia of the media is seen between the points indicated by arrows. At these points the internal and external elastic laminae fuse to form a single lamina separating the adventitia and the proliferated fibrous tissue that occludes the lumen of the vessel.

FIG. 21. Case 6. Transverse section of a muscular pulmonary artery (diameter 900 μ), showing the healing stage of arterial necrosis.

FIG. 22. Case 1. Transverse section of muscular pulmonary artery (diameter 290 μ). Recanalization has occurred in the lumen of the vessel, which is blocked by fibroelastic tissue proliferated from the intima. The internal elastic membrane is very thick.

in patients with mitral stenosis and by Cosh[11] in patients with patent ductus arteriosus and severe pulmonary hypertension, while "medial hypertrophy and intimal sclerosis" have been reported in patent ductus arteriosus with pulmonary hypertension,[7, 8, 10-12, 64] in Eisenmenger's complex,[30, 31] in mitral stenosis,[25-28] and in idiopathic pulmonary hypertension.[33, 34]

We have observed pulmonary vascular necrosis in only 2 of a series of 17 patients with hypertensive pulmonary vascular disease (fig. 21); both suffered from idiopathic pulmonary hypertension and neither showed an increased vascularity of the lung, such as was observed in case 1 (fig. 19) due to dilated branches of the muscular pulmonary arteries. A survey of other

descriptions of patients with severe pulmonary hypertension suggests that arteriolar necrosis and increased pulmonary vascularity are distinct histologic changes associated with different clinical subgroups and that the illness is of short duration when there is arterial necrosis, as in the patients described by Symmers[59] and Aitchison and Richmond.[60] When pulmonary artery blood pressures exceed systemic arterial blood pressures, it seems probable that the nutritive blood supply to the pulmonary vessels through vasa vasorum from the bronchial arteries will be impaired and that this ischemia is the cause of arterial necrosis. The highest pulmonary artery blood pressures occur in patients with idiopathic pulmonary hypertension and mitral stenosis, where it is not possible for a direct shunt into the systemic circulation to act as a safety valve, as in patients with congenital septal defects. Arterial necrosis has been much more commonly reported in patients with severe pulmonary hypertension who were suffering from idiopathic pulmonary hypertension or mitral stenosis than in others with associated congenital anomalies; its presence suggests a lack of adaptation to pulmonary hypertension. In patients with a congenital cardiac defect acting as an escape valve, Wood[22] and Cutler and his associates[24] found that the course of hypertensive pulmonary vascular disease was of longer duration than in idiopathic pulmonary hypertension. In some patients there may be increased pulmonary vascularity caused by bronchopulmonary anastomoses or by dilated branches of muscular pulmonary arteries, as in case 1 and in the case of Dammann and his colleagues.[64] These changes probably represent an adaptation to pulmonary hypertension, since patients with such vascular lungs have usually a long history of pulmonary hypertension and are frequently polycythemic, while those with arterial necrosis have a rapidly progressive course and are often anemic. Lendrum[65] and Braunstein[66] found arterial necrosis in patients with pulmonary hypertension and thought that it was in part an allergic response which Lendrum terms "hyperergic vasculosis." Although pulmonary arterial necrosis certainly occurs as an allergic response in such conditions as polyarteritis nodosa, there appears to be no reason why the abnormally high pulmonary arterial blood pressure should not be accepted as the sole etiologic factor when necrosis develops in hypertensive pulmonary vascular disease. Hultgren and his associates[12] found arterial necrosis and tubercles scattered throughout the lung in a girl who had suffered from patent ductus arteriosus complicated by pulmonary hypertension and considered these to be due to coccidioidomycosis. Similar appearances have, however, been found in a patient with idiopathic pulmonary hypertension[46] where there was no suggestion of coccicioidomycosis; these were due to adventitial reaction around areas of medial necrosis. Medial necrosis of the large elastic pulmonary arteries has been reported in patients with patent ductus arteriosus and pulmonary hypertension.[7, 14] Although this change may have been due to impairment of the nutritive bronchial blood supply by pulmonary hypertension, the aorta was also affected in the case of Whitaker, Heath, and Brown[14] and medial necrosis of the aorta is usually a congenital abnormality.

Atheromatous deposits may occur in the elastic pulmonary arteries of patients with hypertensive pulmonary vascular disease and have been reported with patent ductus arteriosus,[7, 10, 14] with Eisenmenger's complex,[19] with a ventricular septal defect,[20] and with mitral stenosis.[27, 29, 67] Although atheroma is a normal degenerative process, these reports indicate an abnormal association between pulmonary hypertension and this change. Thrombosis may occur in the elastic and muscular pulmonary arteries of patients with hypertensive pulmonary vascular disease and has frequently been reported with patent ductus arteriosus and pulmonary hypertension.[12, 14] It is difficult to accept this thrombosis as embolic in origin, and it is most probably the result of increased blood viscosity and stasis.

By creating artificial shunts from the systemic to the pulmonary circulation in dogs, Ferguson and Varco[68] were able to induce medial hypertrophy in the muscular pulmonary arteries and the development of a muscular media in the pulmonary arterioles identical

with the definitive histologic features of hypertensive pulmonary vascular disease. When Harrison[69] and Barnard[70] caused pulmonary hypertension experimentally in rabbits by injecting autogenous blood clots, they failed to produce changes pathognomonic of hypertensive pulmonary vascular disease, but found intimal occlusive lesions and medial atrophy. These changes were similar to lesions seen by us in a patient with lymphangitis carcinomatosa, in whom the pulmonary hypertension was thought to be of too short a duration to produce the appearances usually found with severe pulmonary hypertension. Although changes characteristic of hypertensive pulmonary vascular disease did not result from pulmonary hypertension experimentally induced by pulmonary emboli, they were present in a patient with recurrent pulmonary embolism studied in the Regional Cardiovascular Centre in Sheffield.

Although the term "Ayerza's disease" is still widely used for cyanosed patients suffering from heart failure secondary to lung disease, it is difficult to understand the popularity of such an indefinite diagnosis. Brenner[58] reviewed the history of "Ayerza's disease" and found that in 1901, Ayerza, of Buenos Aires, described in an unpublished clinical lecture, a case of heart failure with such marked cyanosis that the patient was almost black—a cardiac negro. At autopsy dilatation of the bronchi, peribronchitis, and dilatation and hypertrophy of the right atrium and ventricle were found but the pulmonary vessels were not mentioned. According to Brenner, Marty in 1909 described a similar case as "Ayerza's disease" and it was Arrillaga[71] who first commented in such patients on pulmonary arterial lesions, which he later (1924) thought were syphilitic in origin. The relative importance of chronic lung disease, syphilis, and pulmonary vascular lesions in "Ayerza's disease" was never defined. Brenner found that this term was given a different significance by every writer, and he thought that the lesions in the reported cases were merely those of chronic pulmonary disease and right ventricular hypertrophy. It seems probable that the vascular changes noted in the early descriptions of patients suffering from "Ayerza's disease" were those of hypertensive pumonary vascular disease and were not duel to syphilis. A pathologist, inexperienced in pulmonary vascular disease and unacquainted with the characteristic histologic lesions of hypertensive pulmonary vascular disease, recently carried out an autopsy on a patient with a single ventricle and severe pulmonary hypertension, studied at the Regional Cardiovascular Centre, and reported multiple gummata of the lungs! Similarly, Stewart and Crawford[30] thought that the pulmonary blood vessels of a man with Eisenmenger's complex showed evidence of syphilitic change. Some authors have used the term "Eisenmenger's syndrome" to describe all forms of cyanotic heart disease associated with increased pulmonary vascular resistance, pulmonary hypertension, and hypertensive changes in the small pulmonary vessels. The term "Eisenmenger's complex" should be restricted to cyanosed patients with an overriding aorta but without pulmonary stenosis and should not be regarded as equivalent to hypertensive pulmonary vascular disease. The latter term includes patients suffering from idiopathic pulmonary hypertension, atrial septal defect, ventricular septal defect, patent ductus arteriosus, cardioaortic fistula, persistent truncus arteriosus, the Taussig-Bing complex, transpositions, mitral stenosis, and chronic lung disease with severe pulmonary hypertension, as well as those suffering from Eisenmenger's complex.

In addition to histologic changes in the pulmonary vasculature in hypertensive pulmonary vascular disease there are characteristic changes in the heart and main pulmonary arteries. Dilatation of the right atrium and dilatation and hypertrophy of the right ventricle have been reported in idiopathic pulmonary hypertension,[23, 33, 35, 38] in Eisenmenger's complex,[19, 42] in patent ductus arteriosus,[10, 12, 14] and in a patient with a ventricular septal defect with severe pulmonary hypertension.[20] A dilated tricuspid ring was noted by Branwood[34] and Brinton[38] in cases with idiopathic pulmonary hypertension. Many authors have commented that the pulmonary valve and artery were dilated and that there were often deposits of atheroma in the pulmonary vascular tree in

patients with hypertensive pulmonary vascular disease. The weight of the heart is increased, mainly due to right ventricular hypertrophy.[23, 34, 35]

Relation of Histologic Changes in Pulmonary Vessels to Etiology of Pulmonary Hypertension

The histologic appearances of hypertensive pulmonary vascular disease were thought by Edwards[42] to be due to persistence of the fetal state of the pulmonary vasculature with superadded changes due to a raised pulmonary artery blood pressure. Gilmour and Evans[33] considered that patients with severe pulmonary hypertension were congenitally predisposed to this complication by hypoplasia or aplasia of the media of the pulmonary vessels. They thought that intimal hyperplasia was added as a result of a transient rise of pulmonary artery blood pressure due to coughing, which increased pulmonary vascular resistance and caused persistent pulmonary arterial hypertension. The occurrence of histologic changes in patients with mitral stenosis and pulmonary hypertension that are identical with those observed in congenital cardiac lesions complicated by severe pulmonary hypertension suggests, however, that any congenital predisposition to develop pulmonary hypertension is not associated with an anatomic congenital abnormality. Wood[22] noted that severe pulmonary hypertension developed in only 15 to 20 per cent of patients with anomalies potentially capable of producing abnormally high pulmonary artery blood pressures. He suggested that this proportion of the general population was congenitally predisposed to develop hypertensive pulmonary vascular disease but did not postulate any anatomic congenital abnormality of the pulmonary vasculature. It certainly appears that a rise of pulmonary artery blood pressure is capable of stimulating medial hypertrophy in some patients who may be congenitally predisposed to this reaction. The increase in pulmonary vascular resistance following the initial changes further raises the pulmonary artery blood pressure and perpetuates the vicious circle of hypertensive pulmonary vascular disease.

Prognosis

The histologic appearances of the pulmonary blood vessels from patients with hypertensive pulmonary vascular disease suggest that the anatomic changes are irreversible. A lung biopsy from case 5 at the time of mitral valvotomy showed histologic appearances identical with those found at autopsy 2 years later. Preoperatively the pulmonary artery mean blood pressure was 108 mm. Hg; in spite of dramatic subjective improvement after operation, there was still clinical evidence of severe pulmonary arterial hypertension before death. Although Baker and his associates[3] found that pulmonary blood pressures fell after mitral valvotomy, normal levels were not reached in any of their patients. The changes observed may have been entirely due to removal of vasoconstrictor impulses arising from the left atrium or to a fall in the hydrostatic pressure in the left atrium, without any reversal of organic disease in the pulmonary vessels.

When hypertensive pulmonary vascular disease complicates a cardiac anomaly and is associated with an abnormal shunt of blood, the shunt acts as a safety valve that prevents the pulmonary artery blood pressures from rising higher than the systemic blood pressures. Wood[22] thought that the prognosis in patients with an intracardiac shunt was better than in those without a shunt. In our experience with patients with patent ductus arteriosus[14] and atrial septal defect with pulmonary hypertension, surgical closure of such defects has precipitated death. However, all patients with hypertensive pulmonary vascular disease are suffering from a progressive, irreversible condition with a bad prognosis, and death will probably occur from congestive cardiac failure, severe hemoptyses, or suddenly and obscurely.

Summary

Patients with pulmonary artery blood pressures chronically elevated to levels approaching or exceeding systemic pressures, form a distinct clinicopathologic entity for which the term hypertensive pulmonary vascular disease is proposed.

The symptoms and signs of pulmonary hypertension dominate the clinical picture in this

syndrome. Symptoms of severe pulmonary hypertension are breathlessness on exertion, frequent coughs and colds, chest pain of anginal type, blueness of the lips and nails, and abdominal distention and ankle swelling due to congestive cardiac failure. Hemoptysis, hoarseness, jaundice, syncopal attacks, and palpitation occur less commonly.

Signs associated with pulmonary hypertension are giant "a" waves in the jugular venous pulse, a parasternal heave, a systolic lift over the right ventricular outflow tract, a palpable second sound in the pulmonary area, which is loud and closely split on auscultation, a Graham Steell murmur, and a pulmonary systolic click. In addition, central and peripheral cyanosis, clubbing of the fingers, jaundice, the signs of congestive cardiac failure, and cardiac murmurs frequently occur.

The electrocardiogram usually shows clockwise rotation of the heart and the ventricular pattern of right ventricular hypertrophy.

On radiologic examination there is evidence of right ventricular hypertrophy, increased prominence of the pulmonary artery and its main branches, and decreased peripheral pulmonary vascular markings.

Angiocardiography demonstrates a dilated pulmonary artery and a coppicing effect in the small branches of the pulmonary vascular tree. The flow of dye through these dilated vessels is abnormally slow. It allows abnormal flows to be visualized and previously unrecognized cardiac defects to be demonstrated.

Cardiac catheterization shows pulmonary artery blood pressures approaching or exceeding systemic pressures and occasionally reveals intrinsic cardiac defects.

The features of this syndrome are illustrated by descriptions of patients with idiopathic pulmonary hypertension, atrial septal defect, ventricular septal defect, patent ductus arteriosus, Eisenmenger's complex, and mitral stenosis and severe pulmonary hypertension, since these are lesions commonly found underlying hypertensive pulmonary vascular disease.

The definitive pathologic changes in the pulmonary vasculature are a distinct muscular media with 2 elastic membranes in the pulmonary arteriole and medial hypertrophy in the muscular pulmonary artery. Frequently in these vessels there is abnormal proliferation of intimal fibrous tissue with partial or complete occlusion of the lumen, adventitial fibrosis, and medial necrosis. Occasionally there is aneurysmal dilatation of thin-walled branches of the muscular pulmonary arteries.

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Summario in Interlingua

Patientes con pressiones de sanguine in le arterias pulmonar que es chronicamente elevate a nivellos approximante o excedente le pressiones systemic representa un distincte entitate clinico-pathologic pro que le designation "morbo pulmono-vascular hypertensive" es proponite.

Le symptomas e signos de hypertension pulmonar domina le aspecto clinic in iste syndrome. Symptomas de sever hypertension pulmonar es dyspnea post effortio, frequente tusses e rheumas, dolores thoracic del typo anginal, coloration blau del labios e del ungulas, e distension abdominal e tumescentia tarsal como effecto de congestive disfallimento cardiac. Hemoptysis, raucitate del voce, ictero, attaccos de syncope, e palpitation occurre minus frequentemente.

Signos associate con hypertension pulmonar es gigante undas "a" in le pulso del vena jugular, cornage parasternal, un elevation systolic supra le via de effluxo dextero-ventricular, un palpabile secunde sono in le area pulmonar (iste sono es forte e exhibi al auscultation un fission stricte), un murmure de Graham Steell, e un clic systolic pulmonar. In plus, cyanosis central e peripheric, digitos hypocratic, ictero, le signos de congestive disfallimento cardiac, e murmures cardiac occurre frequentemente.

Le electrocardiogramma usualmente revela rotation dextrorse de le corde e le configuration ventricular de hypertrophia aextero-ventricular.

Le examine radiologic revela indicationes de hypertrophia dextero-ventricular, accrescite prominentia del arteria pulmonar e de su

brancas, e decrescite marcas pulmono-vascular peripheric.

Le examine angiocardiographic demonstra un dilatate arteria pulmonar e un effecto pullulative in le parve brancas del arbore pulmono-vascula. Le fluxo de colorante a transverse iste dilatate vasos es anormalmente lente. Assi anormal formas de fluxo deveni visualisabile, e previemente non recognoscite defectos cardiac pote esser demonstrate.

Le catheterisation cardiac monstra pressiones pulmono-arterial que approcha o excede pressiones systemic. A vices illo revela intrinsec defectos cardiac.

Le characteristicas de iste syndrome es illustrate per descriptiones de patientes con idiopathic hypertension pulmonar, defectos atrio-septal, defectos ventriculo-septal, patente ducto arteriose, complexo de Eisenmenger, e stenosis mitral e sever hypertension pulmonar, proque iste lesiones es communmente trovate subjacente a morbo pulmono-vascular hypertensive.

Le definitive alterationes pathologic in le vasculatura pulmonar es un distincte media muscular, con 2 elastic membranas in le arteriola pulmonar, e hypertrophia medial in le arteria pulmonar muscular. Frequentemente on trova in iste vasos un anormal proliferation de histos fibrose intimal con partial o complete occlusion del passage, fibrosis adventitial, e necrosis medial. In certe casos on trova dilatation aneurysmal del brancas de arteria pulmonar muscular le quales se distingue per lor parietes tenue.

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The effect of chronic anemia on the development of interarterial coronary anastomoses has been studied in dogs. Collateral function was estimated by direct retrograde flow measurements from the peripheral circumflex artery. In addition, the physiologic adequacy of collateral function was measured by the electrocardiographic changes resulting from complete occlusion of the circumflex artery. Alterations in these indices that resulted from chronic anemia were established by comparisons with normal dogs.

Severe anemia of 4 weeks' duration results in a significant increase in the functional capacity of interarterial coronary anastomoses.

Spontaneous recovery from chronic anemia induces collateral regression to near normal function after 5 to 8 weeks.

The inadvisability of inducing anemia to expand collateral function in normal human beings is discussed.

MAXWELL

Effects of Sitosterol on the Cholesterol Concentration in Serum and Liver in Hypothyroidism

By MAURICE M. BEST, M.D., AND CHARLES H. DUNCAN, M.D.

With the Technical Assistance of Joan D. Wathen, B.S. and Ursula Jegher

The effects of the administration of the plant sterol, β-sitosterol, on the elevated serum lipids of hypothyroidism and on the cholesterol content of the liver have been investigated. In patients with hypothyroidism sitosterol administration, without dietary restriction, resulted in a reduction of serum cholesterol and other lipids. In the hypothyroid rat the addition of sitosterol to the diet prevented the increase in serum lipids and in the cholesterol content of the liver which otherwise occurs on a high-cholesterol diet.

THE plant sterol, β-sitosterol, has been reported to exert a hypocholesterolemic effect in the cholesterol-fed chick,[1] and rabbit,[2] and in man on a free diet.[3] It presumably acts by interfering with the intestinal absorption of cholesterol.[4]

In hypothyroidism, numerous observers have demonstrated that the plasma cholesterol and other plasma lipids tend to be elevated.[5] In the rat fed thiouracil, Rosenman, Byers, and Friedman[6] observed a much reduced rate of turnover of plasma cholesterol, both excretion and hepatic synthesis being reduced. These alterations in the handling of cholesterol in hypothyroidism might be expected to modify the effects on plasma lipids of sitosterol administration.

The present study compares the effects on serum and liver lipids of sitosterol administration to normal and to hypothyroid rats. The effect on serum lipids of sitosterol administration to myxedematous human subjects has also been studied.

From the Department of Medicine, University of Louisville School of Medicine, Louisville, Ky.

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METHODS

Rat Studies. Male white rats (Holtzman) of approximately 210 Gm. were maintained for 30 days on a commercial feed containing no added iodine (Pillsbury's mix-grain pellets), 1 per cent sodium chloride solution, and tap water, provided ad libitum. The animals were then divided into 6 groups of 4 to 7 each, the groups having similar mean weights. They were housed in mesh-bottomed cages and maintained in an air-conditioned animal room at approximately 75 F. for the duration of the experiment. At the end of this 30-day period of low-iodine intake, the 17 rats in 3 of the groups were subjected to radiation destruction of the thyroid by radioiodine. Each of the animals received 875 μc. of carrier-free I^{131} intraperitoneally. The 14 rats in the remaining 3 groups received no I^{131} and were considered to be euthyroid.

Three experimental diets were prepared as follows: *low-cholesterol*, Purina rabbit pellets plus 5 per cent cottonseed oil; *high-cholesterol*, Purina rabbit pellets plus 5 per cent cottonseed oil plus 1 per cent cholesterol—the cholesterol was dissolved in the warmed cottonseed oil prior to its addition to the rabbit pellets; *cholesterol-sitosterol*, Purina rabbit pellets plus 5 per cent cottonseed oil plus 1 per cent cholesterol plus 5 per cent β-sitosterol—the rabbit pellets were impregnated with the β-sitosterol dissolved in chloroform, the chloroform was removed by evaporation prior to the addition of the cottonseed oil and cholesterol.

Each of the 3 diets was fed to 1 group of normal and to 1 group of I^{131} treated rats. The special diets were started 2 weeks after the administration of the radioiodine, and offered ad libitum for a period of 13 days. Tap water was provided at all times. The diets were well tolerated, none of the animals developed diarrhea, and all appeared healthy throughout the

TABLE 1.—*Effects on Normal and Hypothyroid Rats of the Addition to the Diet of Cholesterol and of Cholesterol Plus Sitosterol**

Thyroid state	Diet	# Rats	Weight change	Serum total cholesterol	Serum lipid phosphorus	Serum total lipid	Liver total cholesterol
			Gm.	*mg./100 ml.*	*mg./100 ml.*	*mg./100 ml.*	*mg./100 Gm.*
Normal	Low cholesterol	4	+33 ± 8.7 (+22–+43)	72 ± 5 (64–76)	7.6 ± .7 (6.8–8.5)	217 ± 27.3 (189–250)	303 ± 6 (297–311)
Normal	1% Cholesterol	5	+35 ± 5.0 (+30–+42)	75 ± 9 (59–81)	6.6 ± 1.5 (5.3–7.9)	254 ± 42.0 (192–310)	1109 ± 285 (872–1558)
Normal	1% Cholesterol 5% Sitosterol	5	+29 ± 10.2 (+17–+43)	68 ± 6 (59–74)	7.2 ± .9 (5.8–8.0)	220 ± 18.5 (208–253)	271 ± 39 (237–333)
Hypo	Low cholesterol	4	−21 ± 2.7 (−18–−23)	88 ± 16 (74–111)	7.6 ± .6 (7.1–8.4)	246 ± 63.5 (192–336)	270 ± 28 (230–293)
Hypo	1% Cholesterol	7	−24 ± 9.3 (−8–−35)	119 ± 25 (81–151)	7.0 ± 1.1 (6.0–8.8)	312 ± 53.8 (250–397)	1625 ± 296 (1044–1914)
Hypo	1% Cholesterol 5% Sitosterol	6	−27 ± 6.5 (−18–−40)	80 ± 13 (66–95)	7.2 ± .9 (5.9–8.3)	233 ± 26.6 (189–266)	281 ± 28 (260–321)

* Values given are the mean, standard deviation (estimated using n − 1) and, in parentheses, the range.

period of study. On the thirteenth day of the special diets, the animals were anesthetized with intraperitoneal amobarbital sodium, blood was obtained by cardiotomy, and the liver and thyroid were removed. The blood was permitted to clot, serum was separated by centrifugation, and total cholesterol, total lipid, and lipid phosphorus were determined within 24 hours. Cholesterol was determined by the method of Abell and associates,[7] lipid phosphorus by that of Zilversmit and Davis,[8] and total lipid by the turbidometric method of de la Huerga and coworkers.[9] The livers were blotted dry, weighed, and digested over night in 20 per cent alcoholic potassium hydroxide. Total cholesterol was then determined by the method of Abell, and expressed as mg./100 Gm. of liver, wet weight.

The destruction of the thyroid glands was confirmed by microscopic examination. Portions of representative livers were fixed in formalin, embedded in gelatin, and stained for lipid with oil red O.

Human Studies. Six patients with myxedema were selected for study. Included were 2 patients with spontaneous myxedema, 2 with post-thyroidectomy myxedema, and 2 with radioiodine-induced myxedema. Beta sitosterol was administered before eating in a total daily dosage of 20 to 25 Gm.; there was no restriction as to the type or amount of food. A placebo preparation was administered during a portion but not all of the control periods. Fasting serum lipids were determined by the previously described methods at intervals of 1 to 3 weeks during control and sitosterol periods.

RESULTS

The results of the animal experiments are summarized in table 1. The addition of 1 per cent cholesterol to the diet resulted in a significant* increase in liver cholesterol in both normal and hypothyroid animals. Some increase in serum total cholesterol and in total lipid was also observed with the 1 per cent cholesterol diet. The increases were greater in the hypothyroid than in the normal rats, but in neither group were they statistically significant.

The further addition of 5 per cent β-sitosterol to the 1 per cent cholesterol diet significantly reduced the liver cholesterol in both normal and hypothyroid rats. In addition to the reduction in liver cholesterol, the hypothyroid rats also displayed a significant lowering of serum cholesterol and serum total lipid as a result of the added sitosterol.

Comparison of the cholesterol-sitosterol fed groups with those on the low cholesterol diet reveals no significant differences in liver cholesterol or in serum lipids. This is true of both normal and hypothyroid groups.

Microscopic examination of the livers showed a pronounced increase in stainable lipid in the liver cells at the periphery of the lobules of the cholesterol-fed rats, both normal and hypothyroid. The further addition of sitosterol prevented this increase in stainable lipid, the sections being indistinguishable from those of animals on the low cholesterol diet (fig. 2).

For the final 13-day period during which the

* Difference of the means considered significant when $p < 2.5$ per cent as estimated by the t test.

TABLE 2.—*Effects on Serum Lipids of the Administration of Stiosterol to Six Hypothyroid Patients**

Subject	Observation (weeks)		Total cholesterol (mg./100 ml.)		Lipid phosphorus (mg./100 ml.)		Total Lipid (mg./100 ml.)	
	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol	Control	Sitosterol
S.M., I^{131} Induced	24	42	363 (±41.5)	305 (±33.2)	16.8 (±0.7)	14.1 (±0.7)	1039 (±99.6)	869 (±84.4)
V.S., Surgical	14	24	315 (±14.3)	266 (±13.1)	13.5 (±1.1)	12.0 (±4.4)	879 (±68.5)	767 (±59.9)
G.K., Spontaneous	8	24	563 (±95.4)	415 (±117)	22.7 (±4.0)	18.6 (±4.9)	1922 (±394)	1583 (±471)
C.M., I^{131} Induced	17	16	246 (±26.8)	216 (±23.6)	11.6 (±1.2)	10.9 (±1.2)	768 (±77.8)	682 (±72.6)
L.H., Surgical	54	4	268 (±32.3)	216 (±14.9)	12.6 (±1.8)	10.6 (±0.6)	812 (±53.5)	662 (±54.9)
J.W., Spontaneous	3	3	257 (±10.5)	175 (±5.0)	12.4 (±0.7)	8.9 (±0.5)	778 (±50.2)	539 (±16.5)

* Values given are the mean and, in parentheses, the standard deviation (estimated using n − 1).

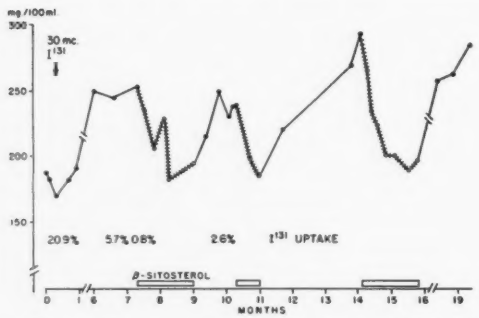

FIG. 1. Changes in the serum total cholesterol in C. M. Following the administration of radioactive iodine the patient developed clinical manifestations of myxedema and elevation of serum cholesterol. Upon 3 separate occasions the administration of sitosterol was accompanied by a reduction in serum cholesterol (cross-hatched line).

special diets were fed, all euthyroid animals gained weight (mean 2.47 Gm./day) while all the I^{131} treated rats lost weight (mean 1.88 Gm./day). These weight changes were not significantly influenced by the addition of cholesterol or sitosterol to the diet.

The patient observations are summarized in table 2. The administration of sitosterol was accompanied by a fall in the mean values of serum total cholesterol, lipid phosphorus, and total lipid. The etiology of the hypothyroidism had no apparent effect on the response to sitosterol. Figure 1 depicts the effects on serum cholesterol of 3 separate periods of sitosterol administration to patient C.M., in whom hypothyroidism was induced by I^{131} in an attempt to alleviate intractable congestive heart failure due to rheumatic heart disease with mitral insufficiency.

DISCUSSION

The administration of β-sitosterol to 6 hypothyroid patients was accompanied by a consistent reduction in serum cholesterol. The mean fall of 20.1 per cent of control level compares with the fall of 15.6 per cent observed in 10 euthyroid hypercholesterolemic patients.[10] Human studies thus indicate that the hypercholesterolemia associated with hypothyroidism is reduced by the administration of sitosterol without dietary modification.

That the greater fall in serum cholesterol in the hypothyroid patients was not due purely to chance is suggested by the results of the rat studies. Under the experimental conditions employed, the addition of 1 per cent cholesterol to the diet of the rats resulted in a 3- to 6-fold increase in the cholesterol level of the liver, the value being significantly higher in the hypothyroid than in the normal animal. If liver cholesterol is referred to total body weight instead of to liver weight, the relative values for the various groups are not appreciably changed.

Although in this small series the increase in serum cholesterol occurring when hypothyroid rats were fed a high cholesterol diet was not statistically significant, the report of Page and

Brown[11] suggests that it would be with a larger series or more prolonged period of feeding. The euthyroid rat fed cholesterol demonstrated essentially no effect on serum cholesterol level. The greater accumulation of cholesterol in serum and liver occurring in the hypothyroid as compared to the euthyroid rat when fed a high cholesterol diet is presumed to be due to the decreased rate of cholesterol excretion or destruction.[6]

FIG. 2. Stainable lipid in the liver of the hypothyroid rat: (*top*) 1 per cent cholesterol diet, (*center*) low cholesterol diet, (*bottom*) 1 per cent cholesterol diet plus 5 per cent sitosterol.

The further addition of 5 per cent β-sitosterol to the diet prevented the increases in liver and serum cholesterol levels, in both normal and hypothyroid rats on a high cholesterol diet. This effect was more pronounced in the hypothyroid rat in which cholesterol feeding produces greater increases. The effect was also much more pronounced in the liver than in the serum.

In the hypothyroid rat, not only cholesterol excretion, but also hepatic synthesis of cholesterol is greatly reduced.[6] Under these conditions of decreased rate of turnover of cholesterol, one would expect changes in the amount of cholesterol absorbed from the intestine to have an augmented effect on serum and liver levels. Since sitosterol interferes with the absorption of cholesterol from the digestive tract,[4] its increased hypocholesterolemic effect in hypothyroidism is understandable.

SUMMARY

In 6 patients with hypothyroidism the preprandial administration of β-sitosterol in the total daily dosage of 20 to 25 Gm. without dietary restriction, resulted in a mean reduction of serum total cholesterol of 20.1 per cent of the control level.

In both the normal and the hypothyroid rat, the addition of 5 per cent β-sitosterol to the diet prevented the increase in liver cholesterol and stainable lipid which otherwise occurred on a 1 per cent cholesterol diet. Sitosterol also prevented the rise in serum total cholesterol and total lipid which occurs in the hypothyroid rat fed a 1 per cent cholesterol diet.

The reduction in serum and liver cholesterol levels resulting from the interference by sitosterol with the intestinal absorption of cholesterol is augmented by the decreased rate of turnover of cholesterol in the hypothyroid state.

SUMMARIO IN INTERLINGUA

In sex patientes con hypothyroidismo le administration preprandial de beta-sitosterol in total dosages diurne de 20 a 25 g, sin restriction dietari, resultava in un reduction median del total cholesterol seral de 20,1 pro cento del nivello de controlo.

In rattos normal e in rattos hypothyroide, le

addition al dieta de 5 pro cento de beta-sitosterol preveniva le augmento de hepatic cholesterol e lipido colorabile que occurreva alteremente con un dieta a 1 pro cento de cholesterol. Sitosterol etiam preveniva le augmento del total cholesterol seral e del total lipido seral que occurre in rattos hypothyroide recipiente un dieta a 1 pro cento de cholesterol.

Le reduction del nivellos seral e hepatic de cholesterol, resultante ab le obstruction per sitosterol in le absorption intestinal de cholesterol es augmentate per le reducite passage de cholesterol que es characteristic del stato hypothyroide.

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Joyce, J. C.: Dextrocardia, Situs Inversus, and Twinning. Brit. M. J. **2:** 950 (Oct. 15), 1955.

Four instances of situs inversus are described in which, although none was a twin, a strikingly high incidence of twinning occurred in the family: (1) both parents twins; (2) grandfather and grandmother twins; a sister and uncle begat 1 and 3 sets of twins; (3) father a twin, paternal grandmother had set of twins by each of 2 husbands; (4) mother twin, a first cousin begat 2 sets of twins.

Reference is made to the work of Ruud and Spemann (1922) who produced situs inversus through division of amphibian eggs. The twin derived from the right side showed a special tendency to develop this abnormality.

McKUSICK

Anatomic and Pathologic Studies in Ventricular Septal Defect

By Luis M. Becu, M.D., Robert S. Fontana, M.D., James W. DuShane, M.D., John W. Kirklin, M.D., Howard B. Burchell, M.D., and Jesse E. Edwards, M.D.

In a necropsy study of 50 cases of ventricular septal defects, the anatomic position and relations of ventricular septal defects, the causes of and ages at death, and association of ventricular septal defects with other cardiovascular malformations were determined. The present availability of surgical closure of ventricular septal defects makes this information of practical significance.

THE present availability of surgical closure of ventricular septal defects renders a number of questions particularly pertinent. Some of these may be answered by pathologic studies and clinicopathologic correlations. Such studies are proper even though there is inherent selection of cases among those included in a pathologic series. These studies provide information concerning the anatomic position and relations of ventricular septal defects, the causes of and ages at death, and the association of ventricular septal defects with other cardiovascular malformations. The present report is a necropsy study of 50 cases of ventricular septal defect. Surgical procedures designed to close the defects had not been done in any of the patients. An attempt is made to throw additional light on these problems.

Methods and Materials

A series of normal hearts was studied to determine the main anatomic landmarks of the ventricular septum.

A study then was made of 50 hearts that had defects of the ventricular septum. Forty were from patients dying at the Mayo Clinic and 10 were sent to the laboratory of pathologic anatomy from other sources. The series represented all specimens in our pathologic collection with ventricular septal defects in which it was the only congenital malformation of the heart and great vessels or in which other anomalies, such as atrial septal defect or anomalies of the aortic-arch system, were coincidental. Not included in this study were cases in which a ventricular septal defect was part of a recognized complex of related anomalies, such as the tetralogy of Fallot, persistent truncus arteriosus, complete transposition of the great vessels, or subaortic stenosis with biventricular origin of the pulmonary trunk.

Each specimen was classified on the basis of the location of the ventricular septal defect according to the scheme to be presented in the next section of this paper.

The diameter of the defect and the diameter of the aorta at the level of the valve were measured in each specimen. The ratio of their relative sizes was useful in defining the size of a given ventricular septal defect irrespective of the age of the patient and the size of the heart.

The cause of death in each case was designated as either related or unrelated to the congenital malformation of the heart. The immediate causes of death in the former group were heart failure and bacterial endocarditis. Although heart failure was considered to have affected both ventricles, the cases with this complication could be subdivided further according to the predominant picture: predominantly left ventricular failure was considered to be manifested in the cases showing pulmonary congestion and edema, whereas predominantly right ventricular failure was considered to exist in cases having peripheral edema, serous effusion, and chronic passive congestion of the liver.

The results of the pathologic studies are presented in 2 sections. The first involves those cases in which the ventricular septal defect was not associated with other cardiovascular anomalies (group A). The second section deals with those cases in which the ventricular septal defect was associated with other coincidental, congenital malformations of the heart or great vessels (group B).

From the Mayo Foundation and the Mayo Clinic, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

This paper incorporates, by abridgment, a portion of the thesis submitted by Dr. Fontana to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

Anatomic Considerations

The 50 hearts included in this study were classified according to the region of the ventricular septum involved by the defect into 2 major groups. In the first group, the defects involved regions of the ventricular septum related to the ventricular outflow tracts; in the second group, the involved regions were not in the ventricular outflow tracts. Lesions in the first group are commoner and, therefore, of greater surgical interest.

Defects Related to the Ventricular Outflow Tracts

Of the 50 hearts, 40 had defects involving this region. The outflow portion of the right ventricle is defined in this study as that part which lies between the pulmonary valve above and the nearest portion of the tricuspid valve below. The inflow portion lies posterior and caudal to the outflow tract.

As seen from its right ventricular aspect, the portion of the ventricular septum related to the ventricular outflow tracts is convex and extends from the tricuspid ring inferiorly and posteriorly to the annulus fibrosus of the pulmonary valve superiorly and anteriorly. This becomes clearer if it is recalled that, as the heart lies in situ, this aspect of the ventricular septum, when viewed from its right ventricular side, rises anteriorly as well as cephalad from the tricuspid ring to the pulmonary valve.

Four major anatomic landmarks of the outflow tract of the right ventricle may be considered (fig. 1*a*). These are (1) the tricuspid ring, (2) the papillary muscle of the conus, (3) the crista supraventricularis, and (4) the annulus fibrosus of the pulmonary valve. It is apparent that nearly all of the septum viewed surgically through the usual incision for right ventriculotomy is related to the ventricular outflow tracts.

The papillary muscle of the conus may be defined as that point of the septal wall of the right ventricle into which insert the chordae tendineae corresponding to the left half of the anterior tricuspid leaflet and the anterior half of the septal leaflet of this valve. At this point is usually located a small broad-based papillary muscle that is readily identifiable, lying about at right angles to the long axis of the right ventricular outflow tract. In some hearts, particularly when the right ventricular chamber is dilated, the chordae tendineae appear to insert directly into the septal wall rather than into a recognizable specialized papillary muscle. It must be stressed, however, that a constant phenomenon is the convergence to the ventricular septum of the chordae tendineae corresponding to the left half of the anterior leaflet of the tricuspid valve and the anterior portion of the septal leaflet.

The crista supraventricularis may be described as a prominent muscular bundle that arches across the uppermost portion of the outflow tract of the right ventricle. Its right anterior limb originates in the anterior wall of the right ventricle approximately at the level of the tricuspid ring. From this point it arches upward and to the left, to pass across the upper wall of the outflow tract between the papillary muscle of the conus below and posteriorly and the pulmonary valve above and anteriorly. The left limb of the crista supraventricularis continues from under the pulmonary valve downward along the ventricular septum.

As seen from its left ventricular aspect, the portion of the ventricular septum related to the ventricular outflow tracts is concave and extends from the point where the anterior mitral leaflet joins the ventricular septum posteriorly to a point located below the midportion of the left aortic cusp* anteriorly (fig. 1*b*).

Along its entire upper border, the left ventricular aspect of the outflow portion of the ventricular septum is related to the aortic valves; therefore, regions in it can be described as the tissue lying beneath a given portion of the corresponding aortic cusp. The adjacent halves of the left and posterior aortic cusps are not related to the ventricular septum, being continuous with the anterior mitral leaflet.

It is helpful for the surgeon to recognize

* In this discussion, the right and left aortic cusps correspond to the aortic sinuses from which the right and left coronary arteries, respectively, arise. The posterior cusp is the noncoronary cusp.

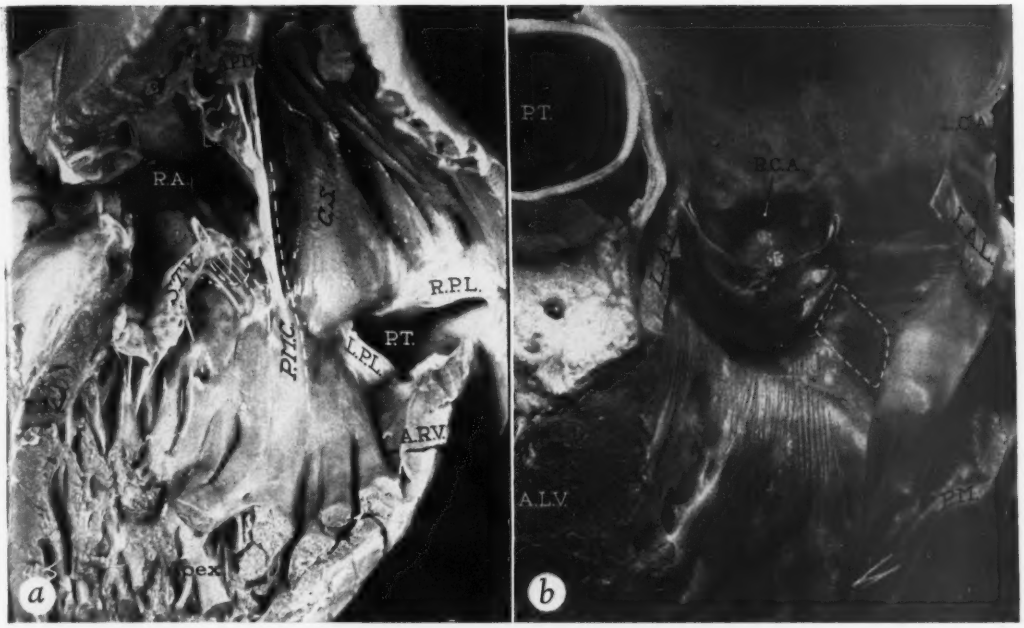

FIG. 1. Anatomic features of the normal ventricular septum.

a. Right ventricular aspect. The septal leaflet of the tricuspid valve (*S.T.V.*) demarcates the junction of the right atrium (*R.A.*) and the right ventricle; retracted upward to show the membranous portion of the ventricular septum (hatched circle). Anterior and superior to this is the papillary muscle of the conus (*P.M.C.*). From this muscle, chordal tissue extends to the adjacent portions of the septal and anterior tricuspid leaflets. Superior and anterior to the papillary muscle of the conus lies the crista supraventricularis (*C.S.*). In a cephalad and anterior position lies the pulmonary valve. *P.T.* = pulmonary trunk; *R.P.L.* = right pulmonary leaflet; *L.P.L.* = left pulmonary leaflet; *P.R.V.* = posterior right ventricular wall; *A.R.V.* = anterior right ventricular wall; *A.P.M.* = anterior papillary muscle of the tricuspid valve. The dotted vertical line corresponds to the center of the right aortic leaflet, which lies beyond this level.

b. Outflow tract of the left ventricle and aorta. The membranous septum (*M.*) lies inferior to the commissure between the posterior (*P.*) and the right (*R.*) aortic leaflets and a portion of the posterior aortic leaflet. The membranous septum also lies anterior and in contact with the anterior face of the anterior mitral leaflet (*A.M.*). The left aortic leaflet (*L.A.L.*) has been sectioned in opening the aorta. *P.M.* = posterior mitral leaflet; *A.L.V.* = anterior left ventricular wall. *L.C.A.* = ostium of left coronary artery. *P.T.* = pulmonary trunk.

that most of the outflow tract of the right ventricle and the pulmonary valve lie more superior (cephalad) and anterior than do the outflow tract of the left ventricle and the aortic valve when the heart is in situ. For this reason, the left extremity of the tricuspid ring lies at approximately the same horizontal plane as does the aortic valve at the posterior aortic leaflet.

In its right ventricular aspect the outflow tract of the ventricular septum may be divided into 2 regions. One lies posterior and inferior to the crista supraventricularis and extends between it and the tricuspid ring, and the other extends superiorly and anteriorly from the crista supraventricularis to the annulus fibrosus of the pulmonary valve.

Defects Involving the Region Posterior to the Crista Supraventricularis. The region of the right ventricular outflow tract lying inferior and posterior to the crista supraventricularis deserves particular attention because it is most commonly involved by ventricular septal defects. The ventricular septal defect

was in this region in 36* of the 50 hearts in this study.

These lesions are usually classified as "membranous ventricular septal defects," but it was apparent from this study that such a designation is not an adequate descriptive name. The membranous portion of the ventricular septum is seen from the left ventricle as a small zone lying beneath the commissure between the posterior and right aortic cusps and the adjacent portion of the posterior cusp. It cannot be seen when the interior of the right ventricle is viewed in the usual perspectives unless the tissue of the septal leaflet of the tricuspid valve is retracted upward.

While most of the defects are related to the membranous portion of the septum, it is exceptional for a ventricular septal defect to be restricted to this membranous portion. In almost all of our cases, the defect either did not involve the membranous portion of the ventricular septum at all or involved varying amounts of this region and, additionally, a proportionately larger zone of the muscular tissue lying superoanteriorly to the membranous septum. It is recognized that the defect in such cases may constitute a failure of union of the membranous and muscular septa rather than absence of these elements. The size of the defect itself was mainly related to the amount of the muscular portion of the ventricular septum that was malformed.

As seen from the right ventricle, the region of the ventricular septum lying immediately posterior and inferior to the crista supraventricularis is overhung by the left half of the anterior leaflet and the anterior half of the septal leaflet of the tricuspid valve. Most of the chordae of this valvular tissue converge toward the apex of the papillary muscle of the conus. The posterior boundary of this region on its right ventricular aspect is the tricuspid ring. The posterior boundary on its left ventricular aspect is the junction of the anterior mitral leaflet and the ventricular septum.

From the right side, the papillary muscle of the conus appears as a prominent landmark within the region being described and serves as a useful point of reference in estimating the size of a given ventricular septal defect. The right and left ventricular relations of defects involving this region are better understood if it is realized that a plane extending at right angles to the septum along the long axis of the papillary muscle of the conus of the right ventricle will run more or less vertically through the middle of the right aortic cusp on the left side and that the crista supraventricularis lies at a level corresponding to the commissure between the right and left aortic cusps. This relationship is noted clearly during open right ventriculotomy for the repair of ventricular septal defects.

In the 36 instances of ventricular septal defect involving the region posterior to the crista supraventricularis, the inferoposterior extremity of the defect was the tricuspid ring or identifiable portions of the membranous septum. The superoanterior extremity of the defect in 20 of these cases did not extend beyond the level of the chordae emanating from the papillary muscle of the conus (fig. 2). These defects were overhung by the septal tricuspid leaflet and were obscured either completely or partially from view unless the septal tricuspid leaflet was retracted superiorly. All except 1 of these defects were small, their diameter being less than the diameter of the aorta. From the left ventricular aspect, these smaller defects were confined to the tissue of the ventricular septum inferior to the right half of the posterior aortic cusp and varying amounts of the adjacent half of the right aortic cusp. Their anterior border did not extend anterosuperiorly beyond a line drawn through the midportion of the right aortic cusp.

In the other 16 of these 36 instances of defects involving the region posterior to the crista supraventricularis, the superoanterior extremity of the defect extended beyond the papillary muscle of the conus to involve the septal tissue lying between it and the crista supraventricularis (fig. 3). In all defects in this series involving tissue between the papillary muscle of the conus and the crista supraventricularis, the aforementioned ratio of the diameter of

* One heart had 2 ventricular septal defects, 1 in this category and the other in the inflow portion of the septum. This explains the total of 51 defects noted in these 50 hearts.

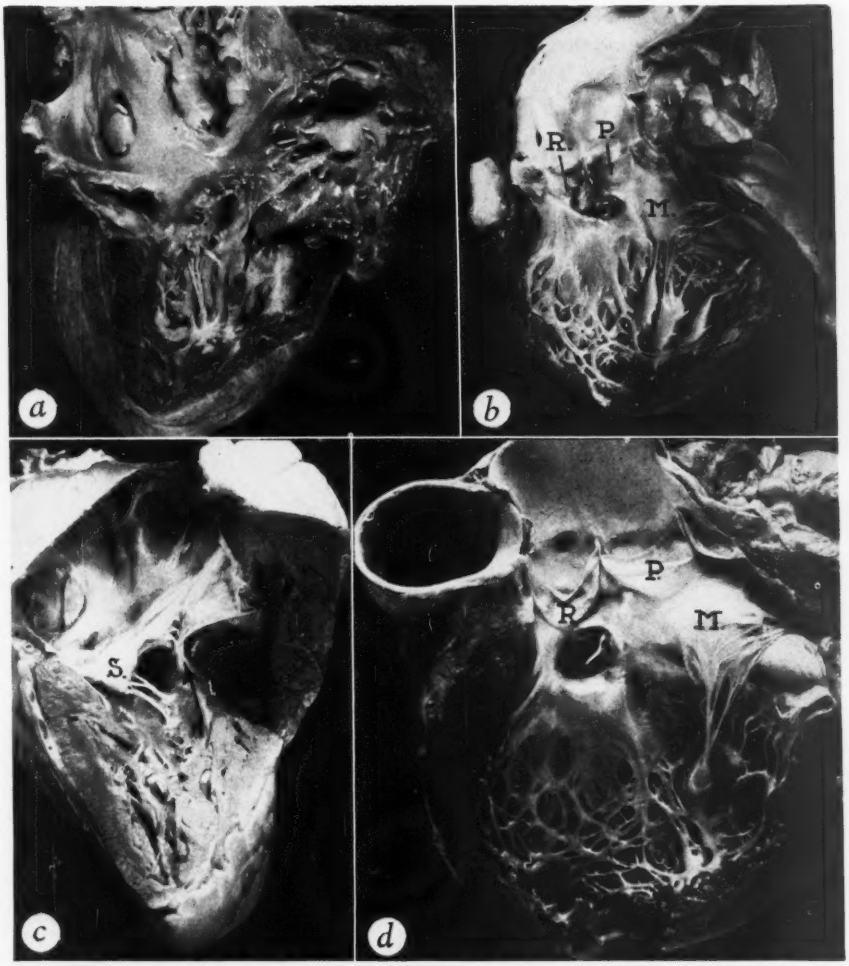

FIG. 2. Ventricular septal defects in relation to the membranous septum and lying behind the papillary muscle of the conus.

a. Right ventricular aspect in a 32-day-old girl. The defect lies partly hidden by the septal leaflet of the tricuspid valve (*S.*) and posterior to the papillary muscle of the conus (point of arrow). This defect involves the membranous septum and muscular tissue anterior to it.

b. Same case, the defect being viewed from the left ventricle anterior to the anterior leaflet of the mitral valve (*M.*) and inferior to the adjacent portions of the right (*R.*) and posterior (*P.*) leaflets of the aortic valve. The anterior extremity of the defect is beyond the membranous septum and involves muscular tissue in this region.

c. Right ventricular aspect in a 33-year-old woman. The defect lies posterior to the papillary muscle of the conus (point of arrow) and is partly hidden by the septal leaflet of the tricuspid valve (*S.*). *d*. Same case, viewed from the left ventricular aspect; the defect lies inferior to the right aortic leaflet (*R.*) and the commissure between the right and posterior (*P.*) leaflets. Membranous septal tissue is present between the defect and the anterior leaflet of the mitral valve (*M.*).

the defect to the diameter of the aortic orifice was 1.0 or more, indicating that the diameter of the defect was equal to or larger than the diameter of the aorta. From the left ventricular aspect, defects with these features involved the septal tissue that lies inferior to the right aortic leaflet and the adjacent half of the posterior aortic leaflet. Thus, these defects

involved the same regions as did the group of small defects previously considered, but also involved the septal tissue that lies between the papillary muscle of the conus and the crista supraventricularis on the right side, and beneath the anterior half of the right aortic cusp on the left.

These anatomic considerations may be

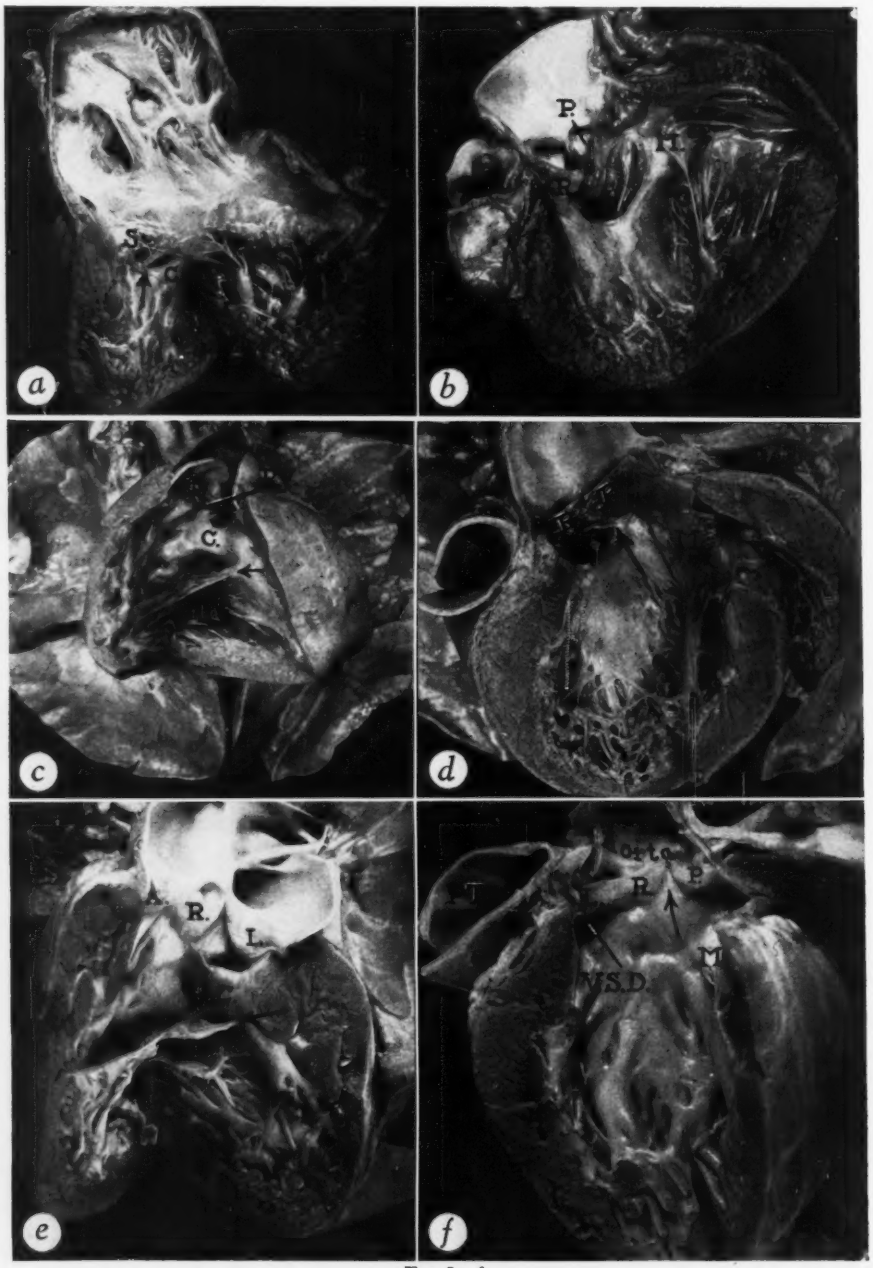

FIG. 3*a–f*

summarized as follows: From the right ventricular aspect, the papillary muscle of the conus lay superoanterior to all defects with small ratios; most defects with large ratios involved tissue extending both anterior and posterior to it. From the left ventricular aspect, most defects with large ratios involved septal tissue lying below the anterior half of the right aortic cusp, whereas no defects with small ratios involved tissue below the anterior half of the right aortic cusp, these lesions being restricted to tissue beneath the posterior cusp and the posterior half of the adjacent right aortic cusp.

In all instances in which the defect involved the septal tissue lying below the anterior half of the right aortic cusp, the aortic leaflets overhung the outflow tract of the right ventricle giving the impression of "dextroposition" of the aorta. This usually did not occur in defects of smaller ratios. In those cases in which the membranous portion of the ventricular septum was entirely lacking, the septal leaflet of the tricuspid valve and the anterior leaflet of the mitral valve became continuous across the posterior border of the defect.

Defects Involving the Region Anterior to the Crista Supraventricularis. The septal tissue that extends from the crista supraventricularis to the annulus fibrosus of the pulmonary valve on the right side corresponds on its left ventricular aspect to the tissue lying below the right half of the left aortic cusp. Four instances of defects involving this region were found among the 50 specimens in this study.

The main features of such defects are their close relationship to the pulmonary valve and their lack of extension inferiorly and posteriorly beyond the crista supraventricularis. The membranous portion of the ventricular septum was intact and normal in appearance in all instances. The upper border of the defect was formed by pulmonary valvular tissue, usually the left cusp. From the left ventricular

FIG. 3. Defects related to the membranous septum and extending superior and anterior to the papillary muscle of the conus.

a. Right side of heart from a 2-day-old boy. The defect is seen through the septal leaflet of the tricuspid valve (*S.*), where it involves the membranous portion of the septum and extends beyond the papillary muscle of the conus (point of arrow) to include the tissue between this region and the inferior edge of the crista supraventricularis (*C.*).

b. Same case, left ventricle. The large defect involves the tissue inferior to the posterior aortic leaflet (*P.*) and the tissue inferior to the adjacent half of the right aortic leaflet (*R.*). The membranous septum is absent. The posterior boundary of the defect is formed by the continuous membrane representing the anterior leaflet of the mitral valve (*M.*) and that portion of the septal leaflet of the tricuspid valve that is seen through the defect from this view.

c. Specimen from a 3-month-old boy. The defect is clearly seen between the crista supraventricularis (*C.*) and the papillary muscle of the conus (point of arrow); it extends posteriorly beyond this region but is obscured by the septal leaflet of the tricuspid valve. *P.V.* = pulmonary valve.

d. Same case, left ventricle. The defect lies inferior to the adjacent halves of the right (*R.*) and posterior (*P.*) aortic leaflets. The membranous portion of the septum is intact, lying between the point of the arrow and the anterior leaflet of the mitral valve (*M.*). These cases illustrate that, when a defect involves the region between the papillary muscle of the conus and the crista supraventricularis, varying amounts of tissue posterior to the papillary muscle of the conus may be deficient, including the membranous septum, but in some instances, as seen in *c* and *d*, the membranous septum may be present.

e. Right ventricle and pulmonary arteries from a 6-month-old girl in whom the defect was anterosuperior to the crista supraventricularis. The defect lies some distance from the papillary muscle of the conus (point of arrow) and is bounded by the crista supraventricularis (*C.*) below and the right (*R.*) and left (*L.*) pulmonary leaflets above. *A.* = anterior pulmonary leaflet. The probe is in a narrow patent ductus arteriosus; an atrial septal defect also was present.

f. Same case. The left ventricular aspect shows the defect (*V.S.D.*) inferior to the left aortic leaflet (*L.*) and some distance from the posterior (*P.*) aortic leaflets, in contrast to cases in which the defect lies posteroinferior to the crista supraventricularis (figs. 3*a* to *d*). *P.T.* = pulmonary trunk; *M* = anterior leaflet of mitral valve.

aspect, these defects lay immediately inferior to the left aortic leaflet and to varying amounts of the adjacent anterior half of the right aortic leaflet.

Comparison of the diameter of the defect and that of the aortic orifice showed that 3 of the defects involving this region had ratios of 1.0 and the fourth had a ratio of 1.3.

Defects Involving Regions Not Related to the Ventricular Outflow Tracts

Among the 50 hearts in this study, 11 had defects of this type (fig. 4). These defects

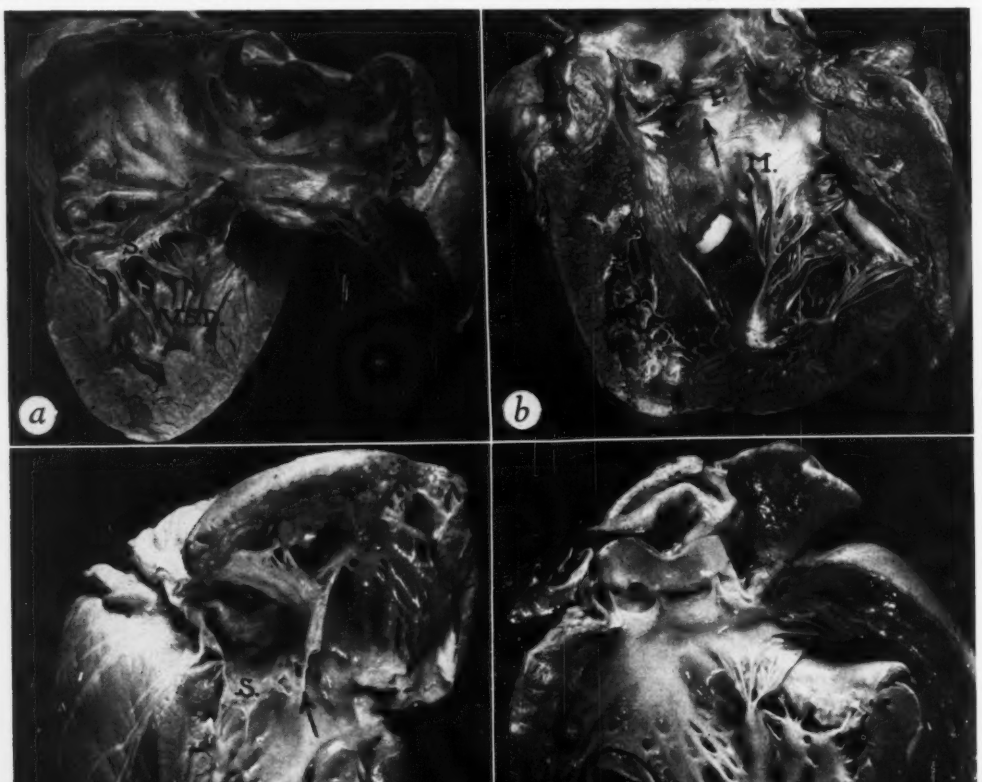

FIG. 4. Defects involving regions not related to the ventricular outflow tracts.

a. Right side of heart of a 51-year-old woman who also had a patent ductus arteriosus and mitral insufficiency. The defect (*V.S.D.*) lies in the muscular portion of the septum inferior to the septal leaflet of the tricuspid valve (*S.*) and far removed from the papillary muscle of the conus (point of arrow) and from the membranous portion of the ventricular septum (dotted circle).

b. Same case. The left ventricular aspect shows the defect in the muscular portion of the septum inferior to the posteromedial commissure of the mitral valve (*M.*). The membranous septum is above the point of the arrow. *R.* = right aortic leaflet; *P.* = posterior aortic leaflet.

c. Heart from a 5½-month-old boy. The defect is in the muscular portion of the septum at the junction of the inflow and outflow portions involving the tissue near the right ventricular apex. The papillary muscle of the conus is at the arrow. *S.* = septal leaflet of tricuspid valve.

d. Same case. From the left ventricular aspect, the defect is seen at the junction of the inflow and outflow portions of the left ventricle.

always were located entirely in the muscular wall of the ventricular septum and were related to the inflow or sinus portion of the ventricles. Two distinct groups could be distinguished.

Defects Related to the Atrioventricular Valves. The defects in this first group were located in the basal portion of the muscular ventricular septum in close relation to the tricuspid and mitral valves. Six such defects were found. The ratios of the diameter of the defect to that of the aortic orifice were 0.4, 0.7, 1.0, 1.0, 1.2, and 1.6. From their right ventricular aspect, these defects opened into the right ventricle close to the tricuspid ring and under the posterior and septal leaflets of the tricuspid valve. From their left ventricular aspect, the defects were in close relation to the base of the posterior papillary muscle of the left ventricle and the posterior leaflet of the mitral valve.

Defects Involving the Apical Portion of the Ventricular Septum. These defects had 1 feature in common in that they were not closely related to any of the valvular structures of the heart. Five hearts had defects of this type, and the ratios were 0.3, 0.5, 0.7, 1.0, and 1.3.

Pathologic Considerations

Group A—Defects Not Associated with Other Cardiovascular Anomalies

Among the 50 cases included in this study were 34 in which the ventricular septal defect was the only cardiovascular congenital malformation. In this group 16 were female and 18 were male. The ages of the patients at the time of death ranged from stillbirth to 55 years, with a median of 2½ months.

Cause of Death. In 19 of the 34 cases in group A (56 per cent), death was attributed to the presence of the defect, whereas death in 15 cases (44 per cent) was considered to be caused either entirely or in part by conditions unrelated to the ventricular septal defect (table 1). For the purpose of this paper, death in such cases was not attributed to the septal defect.

Among the 19 patients dying as a consequence of the defect, 12 (63 per cent) were less than 1 year of age. Death occurred at 4 and 21 months, respectively, in 2 patients and at 5 years in another; the remaining 4 patients died at 14, 18, 33, and 55 years of age. The most frequent cause of death was cardiac failure, which was predominantly left ventricular in type, with pulmonary congestion and edema; it was present in 15 of these 19 patients (79 per cent). These 15 patients included all 12 patients who died in less than 1 year of life. The remaining 3 patients who died with left ventricular failure were 14 months, 21 months, and 14 years of age at the time of death; the last patient also had aortic insufficiency. Two patients aged 5 and 18 years died of bacterial endocarditis, whereas 2 women aged 33 and 55 years died of chronic congestive heart failure.

Types of Defects. The most frequent type of ventricular septal defect in group A involved the outflow regions of the ventricles lying posterior to the crista supraventricularis; 29 of the 34 defects were in this region, 4 involved the inflow portion of the septum, and the

Table 1.—*Relationship of Death to Ventricular Septal Defects Not Associated with Other Cardiovascular Anomalies: Group A*

Age at death*	Location of defects					Totals in each age group	
	Outflow tracts			Inflow tracts			
	Posterior to crista supraventricularis		Anterior to crista supraventricularis				
	Related to death	Unrelated to death		Related to death	Unrelated to death	Related to death	Unrelated to death
0–5 mo.	6	11	1†	2	1	8	13
6–11 mo.	4	0	0	0	0	4	0
1–9 yr.	3‡	0	0	0	1	3‡	1
10 yr. and more	4§	1	0	0	0	4§	1
Totals of types of defects	17	12	1	2	2	19	15

* All deaths related to the ventricular septal defect were caused by left ventricular failure unless indicated otherwise.

† Unrelated to death.

‡ One patient died of bacterial endocarditis at 5 years of age.

§ Two patients died of chronic congestive heart failure at 33 and 55 years of age. One died of bacterial endocarditis at 18 years of age; 1 patient, aged 14 years, had aortic insufficiency associated with the ventricular septal defect; death was caused by left ventricular failure.

remaining lesion was in the outflow tract immediately below the pulmonary valve.

Among the 29 defects involving the region of the outflow tracts posterior to the crista supraventricularis, 18 were of the small type and 11 were of the large type. Of the 4 defects located in the inflow portion of the ventricular septum, 3 were in the apical region and 1 was basal in position, lying just beneath the mitral and tricuspid valves. The anatomic distribution of the defects was about the same in those patients dying of the defects as in those dying of unrelated causes.

Of the 19 patients in group A dying as a consequence of the defect, 7 were more than 1 year of age: 5 of 7 patients had the smaller-type defects in relation to the membranous septum, 1 had the larger type, and the seventh had an inflow defect in the apical region.

Size of the Defect. The median ratio of the diameter of the defect to the diameter of the aorta in the 34 cases comprising group A was 1.0, with a range of 0.2 to 1.7. The median ratio was 1.0 in those cases in which death was related to the ventricular septal defect, whereas it was 0.5 in those cases in which death was not related to the defect. The greatest median ratio (1.1) was noted in those cases in which death occurred before 1 month of age; the median ratio generally was smaller with increasing age at death, being lowest (0.3) at more than 10 years of age, with individual exceptions.

The defects with the largest ratios were those located in the outflow tracts posterior to the crista supraventricularis and involving the septal tissue between it and the papillary muscle of the conus. The median ratio for this type was 1.1, with a range of 1.0 to 1.5. Thus, the diameter of the defect in each of these cases was equal to or larger than the diameter of the aorta.

The defects in the outflow tracts restricted to the septal tissue lying posterior to the papillary muscle of the conus had ratios ranging from 0.2 to 1.7, with a median of 0.5. The largest defect in group A was of this type and was found in the woman who died at the age of 55 years of chronic congestive heart failure. However, most of these defects were small compared to the size of the aorta. The single case in group A in which the defect involved the region anterior to the crista supraventricularis had a ratio of 1.0. The defects involving the inflow or sinus portion of the ventricles had ratios ranging from 0.3 to 1.0, with a median of 0.7.

The 2 patients who died of bacterial endocarditis had relatively small defects, their ratios being 0.3 and 0.6; the 2 patients who died of chronic congestive heart failure had ratios of 0.7 and 1.7. The 15 patients who died of left ventricular failure had a median ratio of 1.0, with a range of 0.2 to 1.5. Three of them had ratios of 0.2, 0.3, and 0.5, while all the others had ratios of 1.0 or more.

Noncardiovascular Anomalies. The 34 patients in group A included 18 (53 per cent) who had some additional congenital malformation not involving the cardiovascular system. These noncardiovascular malformations were of serious nature and caused death in 10 patients; they were numbered among the 15 in group A in whom death was not attributed to the ventricular septal defect. Of these 10 patients, 5 had severe malformations of the central nervous system, 2 had tracheoesophageal fistulas, 1 had exstrophy of the bladder, 1 had a complicated omphalocele, and 1 had infected polycystic kidneys.

In the remaining 8 patients who had noncardiovascular anomalies, the associated lesions were of minor significance; they included supernumerary digits, imperforate anus, cleft palate, congenital hydronephrosis, clubfoot, bilateral double ureter with congenital dislocation of the hip, situs inversus of the spleen and stomach, and diaphragmatic hernia. Some patients had more than 1 malformation. Mongolism was present in 2 instances. Congenital absence of the spleen was not observed in any patient.

Group B—Defects Associated with Coincidental Cardiovascular Malformations

The 50 cases of ventricular septal defect in our series included 16 cases in which other cardiovascular anomalies were present (fig.

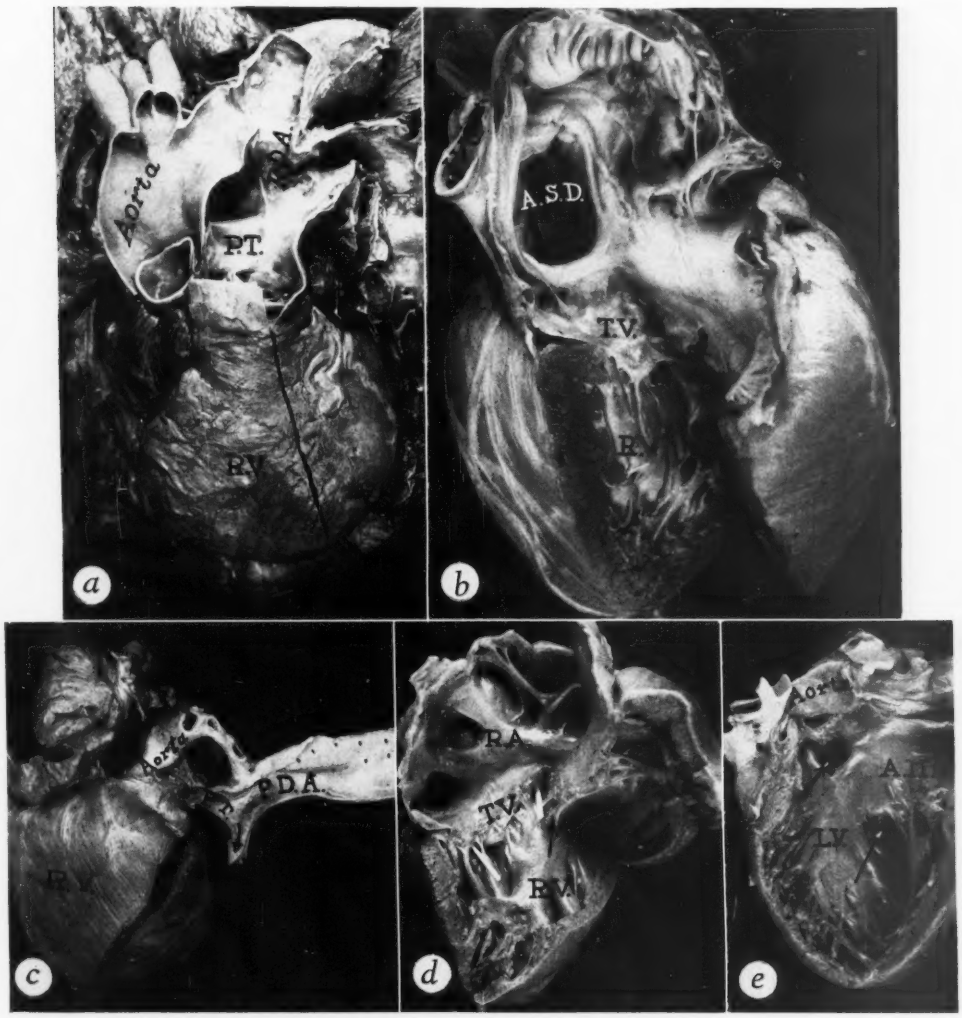

FIG. 5. Malformations associated with ventricular septal defects.

a. The heart and great vessels showing a widely patent ductus arteriosus (*P.D.A.*) in the 51-year-old woman whose ventricular septal defect is illustrated in figure 4 *a* and *b*.

b. The right side of the heart from the 6-month-old girl with an atrial septal defect whose ventricular septal defect and patent ductus are illustrated in figure 3 *e* and *f*. *I.V.C.* = inferior vena cava; *A.S.D.* = atrial septal defect; *T.V.* = tricuspid valve.

c. Heart and great vessels in a 10-day-old girl with a defect located in the muscle of the apical portion of the ventricular septum. Tubular hypoplasia of the aortic arch and a patent ductus arteriosus (*P.D.A.*) are shown.

d. Specimen from a 4-day-old infant with a tracheoesophageal fistula and two ventricular septal defects, which are shown from the right side. One defect involves the tissue in relation to the membranous septum and posterior to the crista supraventricularis. The second defect lies in the muscle in the posterior part of the septum and inferior to the tricuspid valve (*T.V.*). Probes are in the defects. The papillary muscle of the conus is at the point of the arrow.

e. Same case. From the left side, one defect is seen to be centered inferior to the right aortic cusp and the second lies in the muscle inferior to the posteromedial commissure of the mitral valve. *A.M.* = anterior mitral leaflet.

TABLE 2.—*Data in Ventricular Septal Defects Associated with Coincidental Cardiovascular Malformations Together Not Forming Established Complexes*

Region involved by the defect	Case	Age	Ratio*	Associated cardiovascular malformation	Cause of death
Outflow tract					
Posterior to crista supraventricularis	1	21 yr.	0.3	Vascular ring†	Bacterial endocarditis
	2	Stillborn	1.0	Atrial septal defect	Premature stillborn
	3	1 day	1.0	Atrial septal defect	Unrelated to cardiac malformation
	4	3 mo.	0.5	Vascular ring†	Left ventricular failure
	5	5 mo.	1.2	Atrial septal defect	Left ventricular failure
	6	2 yr.	1.0	Coarctation and patent ductus arteriosus	Right ventricular failure
Anterior to crista supraventricularis	7	3 days	1.3	Interruption of aortic arch	Right ventricular failure
	8	3 mo.	1.0	Coarctation of aorta	Left ventricular failure
	9	6 mo.	1.0	Atrial septal defect and patent ductus arteriosus	Right ventricular failure
Inflow tract					
Related to the atrioventricular valves	10	3 mo.	0.4	Patent ductus arteriosus	Left ventricular failure
	11	5 yr.	1.6	Vascular ring†	Left ventricular failure
	12	34 yr.	1.2	Patent ductus arteriosus	Right ventricular failure
	13	51 yr.	1.0	Patent ductus arteriosus and anomalous insertion of chordae, with mitral insufficiency	Right ventricular failure
In the apical region	14	10 days	1.3	Tubular hypoplasia of aorta	Left ventricular failure
	15	14 days	0.7	Coarctation of aorta	Left ventricular failure
Two separate ventricular septal defects, one in the posterior outflow tract and the other in the posterobasal inflow tract	16	4 days	0.8 0.7	Second ventricular septal defect	Unrelated to cardiac malformation

* Ratio of diameter of defect to diameter of aortic orifice.

† Vascular ring characterized by a right aortic arch with retroesophageal segment and left-sided descending aorta. The ligamentum arteriosum was attached to the left pulmonary artery below and to a diverticulum of the aorta at the junction of the right arch and descending aorta above.

5), but together these did not form established complexes.*

Three of these patients died of noncardiovascular causes, while 13 were considered to have died of the ventricular septal defect alone or in association with the additional cardiovascular malformation. The ages at the time of death of these 13 patients ranged from 3 days to 51 years, with a median age at death of 5 months, which is similar to that for the 19 patients in group A who died of the ventricular septal defect.

Pertinent data concerning the 16 patients in group B are given in table 2.

Noncardiovascular Anomalies. Only 2 patients in group B had noncardiovascular congenital anomalies, and death in both instances

* The previously mentioned case with 2 ventricular septal defects, 1 involving the inflow tract and the other involving the outflow tract posterior to the crista supraventricularis, has been placed in group B. This case had no other cardiovascular anomaly but, for convenience of classification, 1 of the ventricular septal defects is considered an anomaly that is additional to the other defect.

was attributed to their presence. One of these patients, who died at 1 day of age, had a large diaphragmatic hernia and congenital hypoplasia of the lung; the other patient died at the age of 4 days of respiratory obstruction after operation for a tracheoesophageal fistula.

Discussion

The ages of the majority of these patients who died as the result of ventricular septal defect with or without associated malformations and whose hearts formed the primary material for this study were strikingly low. As already noted, the ventricular septal defect was considered to be the lesion causing death in 19 of the 34 patients who did not have associated cardiovascular malformations. Twelve of these patients were less than 1 year of age at the time of death.

It was considered that death resulted from the cardiovascular anomalies in 13 of the 16 patients in whom the ventricular septal defect was associated with other significant cardiovascular malformations. Eight of these 13 patients were less than 1 year of age at death. Severe pulmonary edema and hemorrhage were common findings in these young patients.

A standard for measuring the size of the defects was desired in our study. Absolute measurements obviously mean little in comparing the heart of an infant with that of an adult. Therefore, we followed the suggestion of Selzer[1] and compared the size of the ventricular septal defect with the caliber of the aorta. This comparison was expressed as the ratio of the diameter of the defect to the diameter of the aorta.

The patients who died early in infancy of ventricular septal defects had defects, as a group, with larger ratios than did patients who died later in life of bacterial endocarditis. The latter group of patients probably had a significant differential in pressure between the 2 ventricles, and the traumatizing influence of this left-to-right shunt contributed to the ultimate development of bacterial endocarditis. The comparatively small defect, allowing for a differential in pressure between the 2 ventricles and a relatively low pulmonary pressure, probably explains why these patients survived the period of infancy. The latter type of case in the past has been thought to be representative of ventricular septal defect. Even when allowance is made for differences in the percentage of postmortem examinations in different age groups, it is obvious from our studies that this benign type of defect is less common than are defects with larger ratios and in which the ages at death are usually low.

The commonest type of defect, in our experience, was that with a relatively large ratio of the diameter of the defect to the aortic diameter. The majority of patients with such anomalies died in infancy of pulmonary congestion and edema. Such patients probably are like those of other series in whom physiologic studies reveal large left-to-right shunts and various degrees of increased pulmonary arterial pressure. In emphasizing the malignant nature of certain ventricular septal defects, Selzer,[1] Marquis,[2] and Engle[3] probably dealt with similar cases.

A small number of patients in our series had large ratios but did not have evidence of left ventricular failure; they usually were adults. In 1 of these patients, the 33-year-old woman without additional malformations in whom physiologic studies had been done, pulmonary hypertension was demonstrated and the right and left ventricular pressures were essentially equal. Bidirectional shunts of minor proportions had been present. In such cases, large left-to-right shunts and left ventricular failure probably are avoided by the presence of high resistance to pulmonary flow. Such patients might be said to have the Eisenmenger complex. We prefer the more recent approach in classification, as suggested by Selzer and Laqueur,[4] categorizing these cases as instances of large ventricular septal defect with pulmonary hypertension and bidirectional shunts.

The position of the defect appears to make little difference in the behavior of the cardiovascular system. The size of the defect, however, is important.

It is apparent from our study that there is a relatively high incidence (30 per cent) of cardiovascular malformations associated with ventricular septal defects that do not consti-

tute established complexes of malformations. Not included among our 50 cases were examples of the tetralogy of Fallot, persistent truncus arteriosus, complete transposition of the great vessels, the Taussig-Bing complex, persistent common atrioventricular canal, or the complex recently described in which a ventricular septal defect is associated with biventricular origin of the pulmonary trunk and subaortic stenosis.[5] Likewise not included in this series are 2 hearts with ruptured aneurysms of the aortic sinus and ventricular septal defects. The common associated defects in our series were atrial septal defect, patent ductus arteriosus, coarctation or other stenosing lesions of the aortic arch, and vascular rings.

A patient with a ventricular septal defect may have certain physiologic and clinical features that are indistinguishable from those in a patient who has a ventricular septal defect associated with additional cardiovascular malformations. For instance, the association of a wide patent ductus arteriosus with a wide ventricular septal defect may yield a clinical and physiologic pattern indistinguishable from that in a patient who has only a wide ventricular septal defect.[6] Recognition of the similarity between these 2 types of lesions is important in therapy, since it is obvious that treatment is different in these 2 instances.

The association of some type of obstruction in the region of the aortic arch in infants who have ventricular septal defects was strikingly common in our series. It will be recalled that 3 of the 50 patients had classic coarctation of the aorta, 1 had hypoplasia of the aortic arch, and a fifth had interruption of the aortic arch. In patients who have both coarctation of the aorta and ventricular septal defects, the coarctation probably increases the tendency for a left-to-right shunt over what might be expected in the absence of such an aortic obstruction. As in the association of patent ductus arteriosus with ventricular septal defect, it is recognized that the patient with a ventricular septal defect and coarctation may have certain clinical and physiologic features in common with patients having only ventricular septal defects. The essential differences in treatment also are important in such instances.

Three of our 50 patients with ventricular septal defects had an associated right aortic arch. This incidence of 6 per cent is relatively great, although it is less than the incidence of right aortic arch in the tetralogy of Fallot. Three of our patients had atrial septal defects of the usual variety associated with ventricular septal defects. Another patient had these 2 malformations associated with a patent ductus arteriosus. Under such conditions, cardiac catheterization probably would disclose the presence of highly oxygenated blood in both the right atrium and right ventricle. Such a combination of findings would lead to the justifiable consideration in the differential diagnosis of a persistent common atrioventricular canal. Indeed, it might be difficult to distinguish that malformation from an ordinary ventricular septal defect associated with an ordinary atrial septal defect.

A strong tendency appears to exist for defects involving the region of the outflow tracts anterior and superior to the crista supraventricularis to be associated with some form of obstruction of the aortic arch. Two of the 4 patients in this study who had this type of defect also had either coarctation or interruption of the aortic arch. In each of 5 patients who are not part of this study and who are reported on elsewhere[4] as having a complex of malformations, there was a ventricular septal defect anterior to the crista supraventricularis associated with biventricular origin of the pulmonary trunk, subaortic stenosis, and obstruction of the aortic arch. Thus, of 9 patients with defects anterior to the crista supraventricularis, 7 also had an obstructive aortic abnormality.

It is interesting to consider the types of ventricular septal defect encountered when obstruction of the aortic arch is also present. As already indicated, we have studied 10 hearts characterized by obstruction of the aortic arch (including typical coarctation, tubular hypoplasia of the aortic arch, and interruption of the aortic arch) associated with ventricular septal defects. The defect in 7 of

these 10 cases involved that portion of the ventricular outflow tracts anterior to the crista supraventricularis; the defects in 2 cases were in the apical region of the inflow portion of the septum, whereas the defect involved the region of the ventricular outflow tract posterior to the crista supraventricularis in the tenth case.

From our anatomic studies of ventricular septal defects, we are left with the concept that the term "membranous ventricular septal defect" often cannot be applied with accuracy. The greatest contribution to the area of a given ventricular septal defect involving the posterior region of the outflow portion of the septum usually is in the territory of a portion of the muscular ventricular septum, the membranous portion being partially or totally identifiable.

Summary

In 50 cases in which the hearts had ventricular septal defects studied at necropsy, this anomaly was the only cardiovascular malformation in 34 cases (group A); it was associated with 1 or more cardiovascular malformations in the remaining 16 cases (group B), but together these did not form traditionally recognized complexes.

Of the 19 patients of group A in whom death was related to the ventricular septal defect, 12 were less than 1 year of age at the time of death and each of these 12 died of predominantly left ventricular failure. Bacterial endocarditis and predominantly right ventricular failure were the principal causes of death in the patients who died beyond the period of infancy.

Among the 16 patients in group B, 13 were considered to have died of the cardiovascular malformations. Eight patients were less than 1 year of age at the time of death: 6 of them died of left ventricular failure and 2 of right ventricular failure.

Commonly associated cardiovascular malformations included atrial septal defect (4 cases), obstructive disease of the aortic arch (5 cases), patent ductus arteriosus (5 cases) and vascular rings (3 cases).

The 2 oldest patients at the time of death were a 55-year-old woman with only a ventricular septal defect and a 51-year-old woman with ventricular septal defect, patent ductus arteriosus, and anomalous insertion of the chordae tendineae with mitral insufficiency.

Each ventricular septal defect was classified according to the region of the ventricular septum it involved. By far the commonest type of defect was situated in the outflow regions of the ventricular septum.

Summario in Interlingua

In 50 casos in que le necropsia revelava defectos ventriculo-septal del corde, 34 (gruppo A) habeva iste anomalia como le sol malformation cardiovascular, durante que 16 (gruppo B) habeva lo in association con un o plure alteres. Le observate combinationes de malformationes cardiovascular non representava complexos que es traditionalmente recognoscite.

Inter le 19 patientes del gruppo A in qui le morte esseva relationate al defecto ventriculo-septal, 12 habeva minus que un anno quando illes moriva, e in omne iste 12 casos le causa del morte esseva predominante disfallimento sinistro-ventricular. Endocarditis bacterial e predominante disfallimento dextero-ventricular esseva le principal causas de morte in le patientes qui moriva post le periodo del prime infantia.

Inter le 16 patientes del gruppo B, le morte de 13 esseva considerate como resultato de malformationes cardiovascular. Octo patientes habeva minus que un anno de etate al tempore de lor morte. Sex de illes moriva per disfallimento sinistro-ventricular e 2 per disfallimento dextero-ventricular.

Malformationes cardiovascular de commun occurrentia associate esseva inter alteres defecto atrio-septal (4 casos), morbo obstructive del arco aortic (5 casos), patente ducto arteriose (5 casos), e annulos vascular (3 casos).

Le 2 plus vetule patientes al tempore del morte esseva un femina de 55 annos con solmente un defecto ventriculo-septal e un femina de 51 annos con defecto ventriculo-septal, pa-

tente ducto arteriose, e anormal insertion del chordas tendinee e insufficientia mitral.

Omne caso de defecto ventriculo-septal esseva classificate secunde le region del septo ventricular involvite in illo. Le per multo plus commun defecto esseva situate in le regiones de effluxo del septo ventricular.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Austin Flint Murmur. Austin Flint (1812–1886), then Professor of the Principles and Practice of Medicine in the Bellevue Hospital Medical College, New York, first fully described this murmur in a paper "On Cardiac Murmurs" which appeared in the *American Journal of the Medical Sciences* 44 (new series): 29–54 (July), 1862.

"Now in cases of considerable aortic insufficiency, the left ventricle is rapidly filled with blood flowing back from the aorta as well as from the auricle, before the auricular contraction takes place. The distension of the ventricle is such that the mitral curtains are brought into coaptation, and when the auricular contraction takes place the mitral direct current passing between the curtains throws them into vibration and gives rise to the characteristic blubbering murmur. The physical condition is in effect analogous to contraction of the mitral orifice from an adhesion of the curtains at their sides, the latter condition, as clinical observation abundantly proves, giving rise to a mitral direct murmur of a similar character.

"A mitral direct murmur, then, may exist without mitral contraction and without any mitral lesions, provided there be aortic lesions involving considerable aortic regurgitation."

Effects of Estrogen Therapy on Hormonal Functions and Serum Lipids in Men with Coronary Atherosclerosis

By Roger W. Robinson, M.D., Norio Higano, M.D., William D. Cohen, Ph.D., Ronald C. Sniffen, M.D., and Joseph W. Sherer, Jr., M.D.

Middle-aged men with coronary atherosclerosis were studied before and at intervals after initiation of estrogen therapy over a 12-month period. Serum lipid studies during treatment revealed consistent increases in phospholipid and α-lipoprotein cholesterol and decreased β-/α-lipoprotein cholesterol ratios. Concomitant endocrine studies demonstrated the expected testicular depression without apparent detriment to thyroid or adrenal function.

PREVIOUS investigators have demonstrated alterations of the serum lipid patterns with estrogen therapy in coronary atherosclerosis, both in experimental animals and in patients with this disease. In 1949 Eilert[1] noted that estrogen administration to female patients produced a rise in serum lipid phosphorus and a fall in cholesterol, with a consequent decrease in the cholesterol-phospholipid (C/P) ratio. Later, Katz and Stamler[2] showed that estrogens were effective, prophylactically and therapeutically, against cholesterol-induced coronary atherogenesis in cockerels. Barr, Russ, and Eder[3] gave estradiol or Premarin to male survivors of myocardial infarction and showed that this therapy altered the abnormal serum lipid patterns toward normal adult human values. Similarly, Steiner, Payson, and Kendall[4] reported that administration of ethinyl estradiol to 5 male patients and 3 control patients resulted in either a decrease in serum cholesterol or an increase in phospholipid, with resulting decrease in C/P ratio in all cases. Before estrogen therapy could be accepted for more extensive clinical trial, a study was indicated not only of the effects of estrogen on serum lipids but also on various endocrine functions when given over long periods and in large dosage to men.

From the Medical Division and the Biochemical Research Laboratory, The Memorial Hospital, Worcester, Mass.

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Method and Material

A group of 51 men with myocardial infarction have been treated continuously with estrogen for periods of 6 to 48 months (average, 24 months). Of these, 20 middle-aged males (mean age, 50.5 years) were studied before and at intervals up to 1 year after initiation of therapy with 5 to 20 mg. (average, 10 mg.) daily of oral mixed conjugated estrogens (Premarin). This drug was selected for its freedom from production of nausea and vomiting, which permitted long-term administration. Twenty similar patients (mean age, 48.5 years) received placebo tablets and served as a group for comparison. The estrogen-treated and control groups were comparable as to incidence of angina pectoris, myocardial infarction, congestive heart failure, hypertension, and diabetes.

The effects of estrogen therapy were explained to both the patient and his wife, and their consent was obtained for the treatment. This precaution minimized any subsequent psychologic difficulties.

Serum cholesterol was determined with the acid-iron reagent of Zlatkis, Zak, and Boyle,[5] after hydrolysis and extraction according to Abell, Levy, Brodie, and Kendall.[6] In our hands, this technic yielded cholesterol values averaging 53 $\pm$ 1 mg. per cent lower than did the direct method of Zlatkis and co-workers (N = 350; s.d. = 22 mg. per cent). The high intrinsic sensitivity of the acid-iron reaction permitted convenient, routine cholesterol analyses on 0.2 ml. of serum.

Lipid phosphorus was estimated by a micromethod involving re-extraction with petroleum ether[7] of a dried ethanol-ether (3:1) extract of 0.2 ml. of serum, removal of solvent, wet-ashing ac-

cording to Youngberg and Youngberg,[8] and determination of liberated inorganic phosphate according to Fiske and SubbaRow.[9] Lipid phosphorus × 25 was taken as serum phospholipid.

The "α-" and "β-" lipoprotein fractions of serum were separated by zone electrophoresis, by means of the filter paper "sandwich" technic described by Kunkel and Slater.[10] After migration the papers were cautiously air-dried below 60 C., and narrow strips were taken for staining with bromphenol blue (proteins) and oil red O (lipids). The areas on the unstained strips corresponding to the α-lipid (albumin plus α_1-globulin) and β-lipid (β-globulin) zones were removed separately, the lipids were eluted with chloroform-methanol (3:1), the solvent was removed in vacuo, the residues were re-extracted with petroleum ether, and the cholesterol content of aliquots of the final extracts was determined with the acid-iron reagent.

For fractional analysis of urinary 17-ketosteroids, extracts of aliquots of 48-hour urine specimens were prepared by sequential hydrolysis of conjugates with mammalian β-glucuronidase, continuous ether extraction of residual urine made 2N in sulfuric acid, and boiling in 2N acid, as recommended by Lieberman, Mond, and Smyles.[11] Separate ether extracts were prepared after each hydrolysis, combined, washed with 0.1 N NaOH and water to neutrality, and evaporated to dryness under nitrogen. 17-Ketosteroids were fractionated by gradient elution chromatography with ethanol-benzene on moist alumina, according to the method of Lakshmanan and Lieberman.[12] It should be noted that this technic does not separate dehydro*iso*androsterone* from *iso*androsterone,† nor androsterone‡ and etiocholanolone§ from their respective $\Delta^{9\text{-}11}$-unsaturated derivatives.[11] However, artifact formation was minimized by the scheme of hydrolysis and extraction employed, and qualitative sulfuric acid spectra from 220–460 mμ[13] have indicated the presence of only minor amounts of these companion substances in material eluted from the chromatograms.

Testicular biopsies were performed under local anesthesia on 10 individuals before initiation of estrogen therapy, and again after 1 month and 12 months of therapy. Specimens were fixed in 10 per cent formalin solution and stained by conventional and histochemical technics. The results of the histochemical studies will be reported elsewhere. The histologic studies were performed independently.

Thyroid function was evaluated by the oral administration of a tracer dose of 50 μc. of carrier-free I^{131}‖.[14] The measurement of radioactivity over the thyroid gland was taken 24 hours later. Four lead-shielded copper cathode tubes were spaced 90° apart at the circumference of a 90 cm. diameter horizontal circle and connected in parallel to a scaler. The patient was seated so that his thyroid gland was located in the center of this circle, where there was an 18 cm. diameter sphere in which counts varied only within 2 per cent. Background counts varied between 350 and 400/min., allowing all studies to be made at levels of at least 2.5 × background.

Results

The clinical effects of estrogens on males are well known. Changes in pigmentation, skin texture, and growth and distribution of hair have been described, as well as gynecomastia and testicular atrophy.[15] In those patients whose sexual potency was initially intact, this function gradually decreased, disappearing within 1 to 24 months in all patients on a dose of 10 mg. or more of Premarin daily. Some degree of potency has returned to 3 patients who had received 10 mg. daily for 6 to 24 months before withdrawal of therapy. There has been no evidence to date of a return of fertility in these patients, although circumstances of age prevent an adequate appraisal. The most distressing effect to the patients was gynecomastia, which was minimal (tenderness and slight swelling) in most of the patients and moderate in only 2. The tenderness usually subsided within a few months. An unexpected observation was the growth of new scalp hair in 4 bald patients. The only cardiac complication to the therapy was the appearance of pulmonary edema in 2 patients, which did not respond to digitalis and diuretics, but did subside promptly on omitting the estrogen.

It is clear that the control group showed no significant alteration in serum cholesterol (fig. 1) or phospholipid (fig. 2) during the year of observation. The estrogen-treated group showed a decrease of cholesterol, of borderline significance statistically, by the end of 3 months (fig. 1). Figure 2 shows the strikingly significant increase of phospholipid in the treated group, from 207 mg. per cent to 248 mg. per cent at 3 months. This increase was maintained to 12 months. Figure 3 demonstrates that the C/P ratio in the estrogen-treated group, initially 1.30, was significantly decreased to 1.1 at 1 month, further decreased at 3 months to 0.96, and maintained thereafter to 1 year. The

* Δ^5-Androsten-3β-ol-17-one (dehydro*epi*androsterone)

† Androstan-3β-ol-17-one (*epi*androsterone)

‡ Androstan-3α-ol-17-one

§ Etiocholan-3α-ol-17-one (Testan-3α-ol-17-one)

‖ Obtained on allocation from the United States Atomic Energy Commission, Oak Ridge, Tennessee

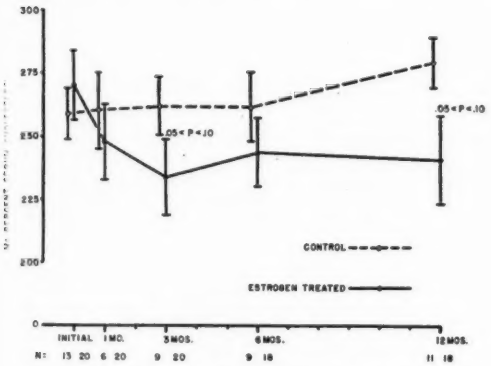

FIG. 1. Mean serum cholesterol levels in estrogen-treated and control groups observed for 12 months. The figures indicate mean values and standard errors of these means.

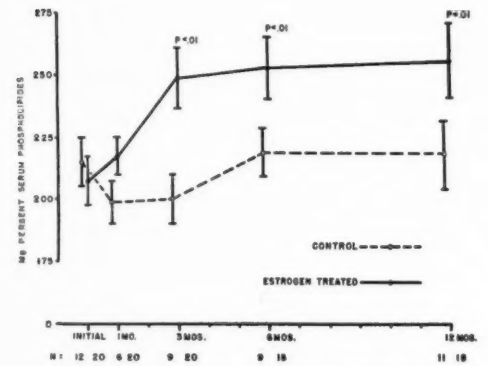

FIG. 2. Mean serum phospholipid levels in estrogen-treated and control groups for 12 months.

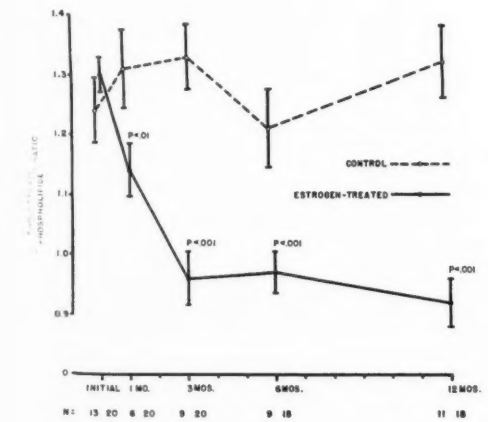

FIG. 3. Serum C/P ratios in estrogen-treated and control groups for 12 months.

C/P ratio of the control group was essentially unchanged.

The distribution of serum cholesterol in the α- and β-lipoprotein fractions as per cent of total cholesterol is shown in figure 4. The control group showed no significant changes during the 1-year period, despite the apparent decrease

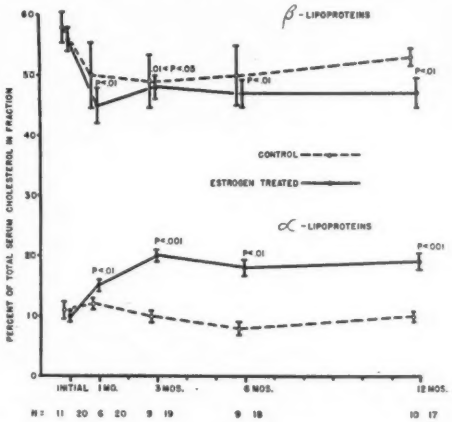

FIG. 4. Distribution of cholesterol in serum α- and β-lipoprotein fractions (separated by zone electrophoresis) in estrogen-treated and control groups for 12 months. Lipoprotein cholesterol calculated as per cent of total cholesterol in each fraction.

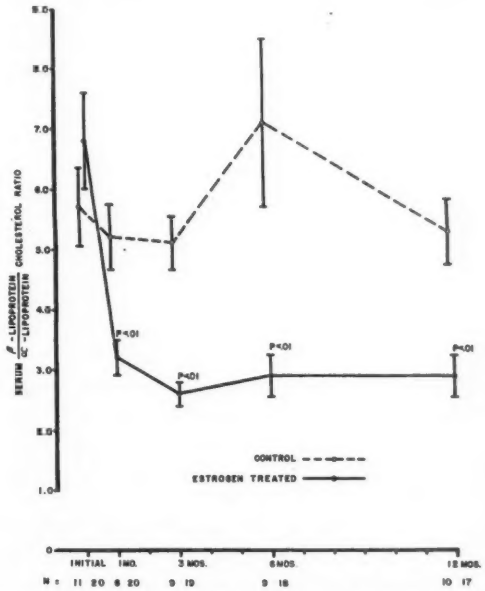

FIG. 5. Serum β-/α-lipoprotein cholesterol ratios in estrogen-treated and control groups for 12 months.

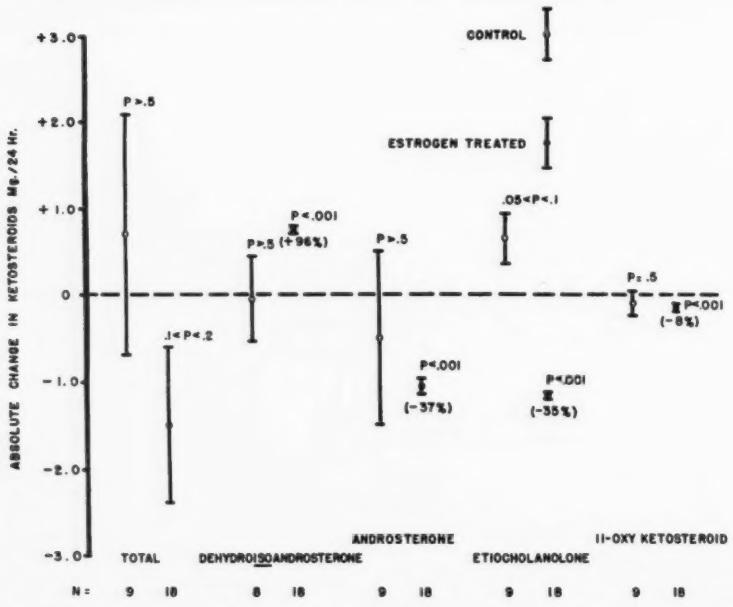

FIG. 6. Aterations in urinary 17-ketosteroid excretion patterns during 1 year of estrogen treatment. Pretrleatment levels and initial values in control group adjusted to zero line.

in the β-lipoprotein fraction. On the other hand, the estrogen-treated group showed a striking rise in α-lipoprotein cholesterol from 10 to 15 per cent in 1 month, a further increase to 20 per cent in 3 months and subsequent maintenance near this level. The cholesterol in the β-fraction showed a significant fall from 56 to 45 per cent in 1 month ($p < 0.01$) that was unchanged thereafter. However, the latter results are of dubious validity, since the control group showed a similar but not significant fall from 58 to 50 per cent in 1 month ($p = 0.1$).

Figure 5 shows the effect of these reciprocal changes upon the ratio of β- to α-lipoprotein cholesterol. There was no significant change of this ratio in the control group, while the ratio in the estrogen-treated group had dropped sharply by 1 month, from 6.8 to 3.2, and was maintained thereafter near 3.0. It is clear that this effect was primarily due to the striking increase in the α-lipoprotein cholesterol fraction.

Figure 6 shows the changes observed in urinary 17-ketosteroids. It will be seen that in all instances the changes observed in the control group did not differ significantly from zero. This was also true of the total 17-ketosteroid output in the estrogen-treated group. However, the daily excretion of dehydro*iso*-androsterone was increased during estrogen therapy from 0.8 to 1.6 mg., while the excretion of androsterone and of etiocholanolone was

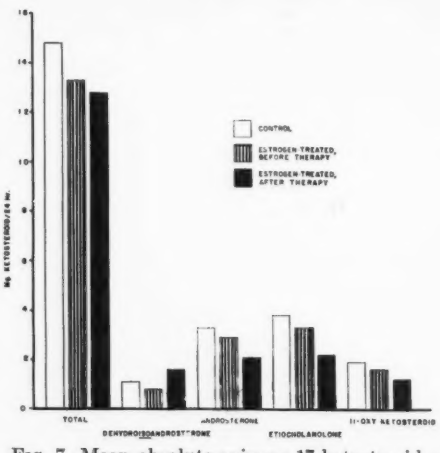

FIG. 7. Mean absolute urinary 17-ketosteroid excretion levels, mg./24 hours, in control and estrogen-treated groups, the latter shown prior to and during therapy.

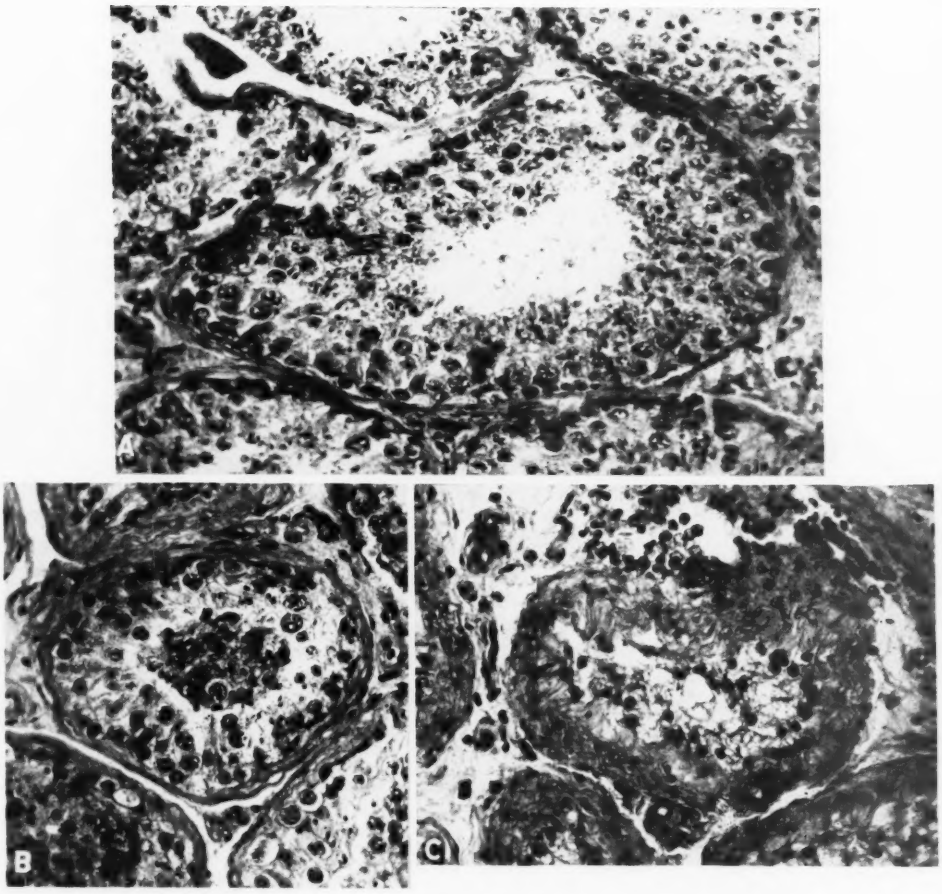

FIG. 8. *A*. Testicular biopsy before estrogen therapy. Normal spermatogenesis. *B*. Testicular biopsy 1 month after institution of estrogen therapy (0.3 Gm. total). Hypospermatogenesis with arrest of spermatocytogenesis at primary spermatocyte level. Moderate thickening of tubular tunica propria. *C*. Testicular biopsy 12 months after institution of estrogen therapy (3.65 Gm. total). Aspermatogenesis with tubules lined by atrophic lipid-filled Sertoli cells. Marked thickening of tubular tunica propria. Leydig cells not identifiable.

markedly depressed (by 37 and 35 per cent, respectively). The 11-oxygenated ketosteroids remained essentially unchanged at approximately 1.5 mg./24 hours. Figure 7 shows the absolute values in milligrams per 24 hours of the total and component ketosteroids recovered after chromatography. The average daily 17-ketosteroid output in the control group was 14.8 mg. and in the treatment group 13.3 mg. before therapy. This remained relatively constant (12.8 mg.) during estrogen treatment.

Histologic studies of testicular biopsies prior to estrogen therapy (fig. 8*A*) revealed normal Sertoli cells, spermatogenesis, and Leydig cells. Serial biopsies during estrogen therapy showed suppression of all cellular activity of the testicle. At 1 month of treatment (fig. 8*B*) there was failure of sperm development, with subsequent suppression of spermatocytogenesis until only a few spermatogonia remained. At this time many tubules were lined only by Sertoli cells. Concomitantly, the tunica propria was thickened by a deposition of collagen and elastic fibrils. After 12 months of therapy

TABLE 1.—*Thyroid Function As Measured by Twenty-four-hour Uptake of Radioactive Iodine before and after Twelve Months of Therapy with Estrogen or Placebo*

Time of study	Estrogen-treated Group		Control Group	
	Initial	12 Months	Initial	12 Months
N	16	12	10	7
Mean Uptake in %	35	39	40	41
Range in %	15–54	26–51	30–46	31–49
Standard error of mean	±2.7	±2.0	±1.9	±3.0
Significance	—	N.S.	—	N.S.

(fig. 8*C*) the tubules were converted into acellular fibrous cords. Regressive changes in the interstitial cells accompanied this tubular atrophy. The regressing cells diminished in volume, tended to become spindle-shaped, and the cytoplasm lost the coarse granulation and vacuolization presumed to be evidence of secretory activity; a few cells contained coarse granules of tan pigment or occasionally a crystalloid. In the final stage, Leydig cells were not identifiable and many collagen fibrils occupied the interstitium.

Table 1 shows the effect of estrogen therapy for 1 year on the 24-hour uptake of I^{131}. Although there was a suggestive increase of the uptake in the estrogen-treated group from 35 to 39 per cent, this change did not prove to be statistically significant ($p = 0.3$).

DISCUSSION

Since gynecomastia proved to be somewhat distressing, especially in the younger age group, surgical removal of the rudimentary male breast glandular tissue has been performed before institution of estrogen therapy in the more recent cases studied. This is a simple procedure done under local anesthesia with replacement of the cutaneous nipple and areola. An excellent cosmetic effect has been achieved, and no breast hypertrophy has followed this procedure. It eliminates the psychologic effects of gynecomastia and avoids any possibility of malignant disease of the breast from estrogen stimulation.

In 3 patients in whom the loss of sexual potency was especially distressing the treatment was stopped. The serum lipids of 1 of these patients promptly reverted to abnormal levels.

It should be noted that in spite of prolonged estrogen therapy the basic masculine psychologic traits of these patients have remained intact.

The development of acute pulmonary edema noted in 2 patients was thought to be due to the sodium- and water-retaining effect of estrogens.[16]

The serum lipid data presented are in general agreement with those of Eilert,[17] Barr,[18] and Gertler, Garn, and Lerman.[19] For example, the mean serum cholesterol level in untreated men with myocardial infarction was reported by Barr to be 259 mg. per cent, and by Gertler and his associates to be 286 mg. per cent. The mean initial value in the present study was 265 mg. per cent. The chief difference from those studies is that the present phospholipid values were lower. This difference is ascribed to the petroleum ether purification employed in this work. It is of interest that Hack[20] has reported that approximately 10 per cent of the serum phosphorus soluble in ethanol-ether is insoluble in petroleum ether but soluble in water. Similar results with ultracentrifugal fractions of serum have recently been reported by Havel, Eder, and Bragdon.[21] The relatively lower phospholipid values of the present study are reflected in the higher C/P ratios.

By paper electrophoresis, significant changes in the percentage of cholesterol in the α- and β-fractions of the lipoproteins were demonstrated during estrogen therapy. It was found that approximately 75 per cent of the total serum cholesterol was recovered in these fractions. In studies now in progress, individual sera have been submitted to zone electrophoresis and ultracentrifugation at a solvent density of 1.063. The β-/α-lipoprotein cholesterol ratios determined by the 2 technics have shown close correspondence. These studies will be reported elsewhere. The change in β-/α-lipoprotein cholesterol ratios was very similar to that reported by Barr using the Cohn microfractionation method no. 10.[18] Barr's ratios changed from 7.8 to 3.7 in 4 weeks and the ratios presented here from 6.8 to 3.2 in 4 weeks. These represent identical decreases of 53 per cent.

It is noteworthy that despite the changes in excretion of individual 17-ketosteroids during estrogen therapy, there was no significant alteration in the mean output of total 17-ketosteroids. The excretion of dehydro*iso*-androsterone, presumably an "in-process" adrenal metabolite (Lieberman and Teich[22]), was increased during estrogen therapy. Similar data have been presented by A. M. Robinson.[23] The decreased excretion of androsterone and etiocholanolone is readily explained on the basis of diminished testosterone production by the Leydig cells of the testes. The serial testicular biopsy studies offer histologic confirmation of this finding. The relative constancy of excretion of the 11-oxygenated ketosteroids, metabolites of adrenal cortical origin, suggests that adrenal cortical function was not suppressed during estrogen therapy.

Thyroid function, as measured by the 24-hour uptake of a tracer dose of I^{131}, was not significantly altered after 1 year of estrogen therapy with the present dosage. Although this seems at variance with the data of Engstrom and Markardt,[24] it should be noted that these investigators administered relatively large doses of diethylstilbestrol (75 to 100 mg. daily) to the 12 men studied. The serum lipid changes observed in the present study, therefore, cannot be ascribed to increased thyroid function.

Insufficient time has elapsed for a mature evaluation of estrogen therapy as a practical, clinical treatment for coronary atherosclerosis. The favorable blood lipid changes must be balanced against the undesirable effects of the hormone on the male patient. Whether the change in blood lipids slows or reverses the process of coronary atherosclerosis must await the findings of long-term studies of large, well-controlled series of patients.[25] Until such time as there is evidence of benefit that outweighs the disadvantages of this treatment, it must be considered an experimental approach to the problem of coronary atherosclerosis.

Summary

Estrogens change the serum lipid patterns of survivors of myocardial infarction, causing a decrease in total cholesterol, an increase in phospholipid, and an increase in α-lipoprotein cholesterol. Consequently, the C/P ratio and the β-/α-lipoprotein cholesterol ratio fall. In general, these changes were seen as early as 1 month, were more pronounced at 3 months, and were maintained thereafter.

Total urinary 17-ketosteroid excretion was not significantly depressed by estrogens; 11-oxygenated ketosteroids were not decreased. Androsterone and etiocholanolone were substantially decreased, presumably due to depressed testicular function. There was a consistent rise in dehydro*iso*androsterone excretion.

Sexual potency gradually decreased and became absent on 10 mg. of Premarin daily. Testicular biopsies showed fibrosis of tubular cells and severe atrophy or complete absence of Leydig cells at 1 year.

Thyroid function, as measured by I^{131} uptake, was not altered by 10 mg. of Premarin daily for 1 year. The observed serum lipid changes could not, therefore, be ascribed to increased thyroid function.

Estrogen therapy of coronary atherosclerosis should still be regarded as an experimental approach to this problem.

Acknowledgment

We acknowledge with thanks the competent technical assistance of Mrs. Katherine Sevier Marsella and Mr. Paul A. Bonenfant, the generous supply of Premarin from Ayerst, McKenna, and Harrison, Ltd., and the critical review of the manuscript by Dr. George V. Mann.

Summario in Interlingua

Estrogenos altera le configurationes del lipidos seral in superviventes de infarcimento myocardial: Illos causa un reduction del cholesterol total, un augmento de phospholipido, e un augmento de cholesterol a lipoproteina alpha. Il occurre per consequente un reduction del proportion C:P e del proportion beta:alpha de cholesterol a lipoproteina. In general iste alterationes esseva notate post non plus que un mense. Illos esseva plus pronunciate post 3 menses. Postea illos remaneva constante.

Le total excretion urinari de 17-cetosteroide non esseva significativemente deprimite per estrogenos. Le cetosteroides 11-oxygenate non

esseva reducite. Androsterona e etiocholanolona esseva reducite a grados considerabile, probabilemente in consequentia de deprimite functiones testicular. Il habeva un augmento regular in le excretion de dishydro*iso*androsterona.

Le potentia sexual decresceva gradualmente e dispareva con 10 mg de Premarina per die. Biopsias testicular monstrava fibrosis de cellulas tubular e sever atrophia o complete absentia de cellulas de Leydig post 1 anno.

Le functiones thyroide, mesurate per le acceptation de I^{131}, non esseva alterate per 10 mg de Premarina per die durante 1 anno. Le observate alterationes de lipido seral esseva assi non ascribibile a augmentos de function thyroide.

Le therapia a estrogeno in atherosclerosis coronari debe ancora esser considerate como un procedimento experimental.

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Fatal Congestive Heart Failure Associated with Cardiac Enlargement of Unexplained Origin

By RICHARD FRANCE, M.D., CLIFFORD W. ATHERTON, M.D., AND WILLIAM L. ALSOBROOK, M.D.

A case of progressive cardiac enlargement of unknown cause in a 22-year-old man is reported. Death from congestive failure occurred 18 months after the onset of symptoms. Postmortem examination showed only cardiac hypertrophy and dilatation as an explanation for the congestive failure.

WHEN a young, adult male with normal blood pressure dies from congestive heart failure, it is only natural to expect the autopsy to show one of the established forms of heart disease. In the present case no explanation for the illness could be found. The clinical course and postmortem findings are reported in the hope that the information may be of aid in the ultimate solution of the syndrome currently known as idiopathic cardiac enlargement.

CASE REPORT

A 22-year-old Caucasian male entered the hospital for his second admission on January 30, 1955, because of severe shortness of breath and died 10 days later from congestive heart failure. The family history was negative for cardiovascular disease except that his 40-year-old mother was said to have had an enlarged heart associated with episodes of shaking, tension, and weakness. There was nothing in the patient's history to suggest syphilis, rheumatic fever, diphtheria, congenital heart disease, hypertension, alcoholism, or malnutrition. In high school he had played both basketball and football as a member of the first team.

On November 4, 1951, at the age of 18, he enlisted in the United States Navy. Roentgenogram of the chest (fig. 1) showed a normal cardiothoracic ratio of 0.50 but what, in retrospect, is considered to be an abnormal prominence of the left ventricle. Because of frequent attacks of tonsillitis, his tonsils and adenoids were removed on May 21, 1953, at the U. S. Naval Hospital, San Diego, California. The heart was considered normal on physical examination at that time. However, an X-ray film of the chest taken several days before operation was, at a later date, compared with the induction film. This comparison was made on August 28, 1953, by F. H. Holmes, Lt. Cdr. M.C., U.S.N., Roentgenologist, U. S. Naval Hospital, Oakland, California. He stated that study of the 2 photofluorograms showed a progressive increase in the size of the heart and that the film of May 21, 1953, taken at the time of tonsillectomy, showed cardiac enlargement. The operation was without complication and the patient was returned to duty aboard a destroyer.

For the next 7 weeks he considered himself in excellent health. However, on July 6, 1953, he fell a distance of 2 decks, striking his left shoulder and back and suffering a momentary loss of consciousness. From that time on he noticed increasing shortness of breath on exertion and, on August 10, 1953, was admitted to the U. S. Naval Hospital, Oakland, California, in acute left ventricular failure. On examination, orthopnea, pulmonary congestion, cardiac enlargement, gallop rhythm, and slight tenderness in the right hypochondrium were present, but peripheral edema and engorgement of neck veins were not seen. He responded satisfactorily to bedrest, oxygen, digitalis, and mercurial diuretics, so that at the end of a month he was symptom-free on quiet activity about the ward. During his 4 months of hospitalization the blood pressure varied between 90 and 120 systolic and between 70 and 78 diastolic. Except for a single recording of 99.2 F. by mouth on the first day, there was no fever. The pulse rate decreased from 130 to 80/min. by the end of the second day. No leukocytosis or anemia was noted and the corrected erythrocyte sedimentation rate varied between 8 and 18 mm./hr. Antistreptolysin-0 titers were 125 and 160 Todd units. The electrocardiogram showed a QS of 40 mm. in lead V_3 and a sharply inverted T wave in lead V_6 suggesting left ventricular "strain." An x-ray film of the chest (fig. 2) showed pulmonary artery engorgement and an increase in the transverse diameter of the heart. The cardiothoracic ratio by x-ray decreased from 0.63 to 0.55 with clinical improvement.

From the Medical and Laboratory Services, Thayer Veterans Administration Hospital and the Departments of Medicine and Pathology, Vanderbilt University School of Medicine, Nashville, Tenn.

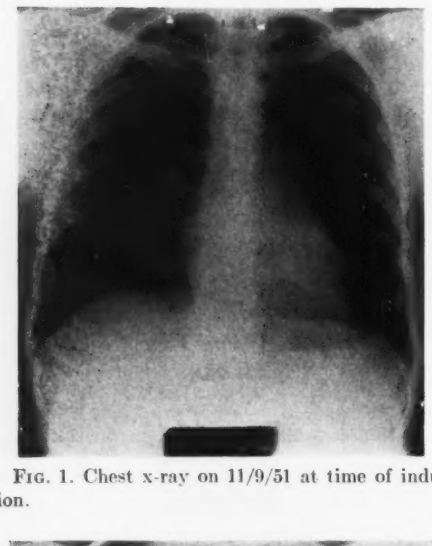

FIG. 1. Chest x-ray on 11/9/51 at time of induction.

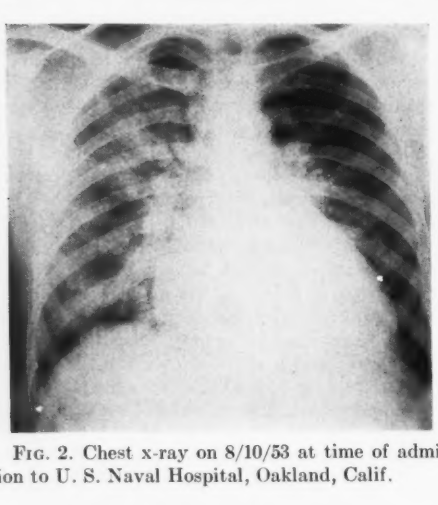

FIG. 2. Chest x-ray on 8/10/53 at time of admission to U. S. Naval Hospital, Oakland, Calif.

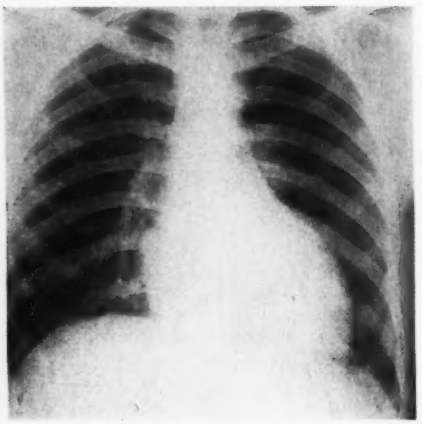

FIG. 3. Chest x-ray on 11/11/53 prior to discharge from U. S. Naval Hospital, Oakland, Calif.

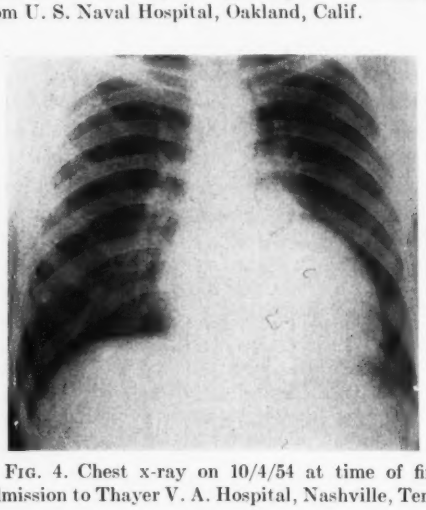

FIG. 4. Chest x-ray on 10/4/54 at time of first admission to Thayer V. A. Hospital, Nashville, Tenn.

At the time of discharge the venous pressure and circulation time were at the upper limit of normal. The x-ray evidence of pulmonary congestion had disappeared (fig. 3). Although on admission the diagnoses considered most likely were rheumatic myocarditis and pericardial effusion, the impression at discharge, after extensive clinical, bacteriologic, hematologic, and serologic examinations, remained "Heart disease of unknown type."

After discharge from the Navy in December 1953, the patient maintained a fair state of health. However, he never regained a normal cardiac reserve and, due to excessive fatigue and exertional dyspnea, was unable to work for more than a few days at a time. No fever or joint pains were noted at any time. On October 2, 1954, he was admitted to Thayer Veterans Administration Hospital, Nashville, Tennessee, for diagnosis and evaluation of his heart disease. Normal blood pressure (108/70), a large left ventricle, a faint, apical systolic murmur, and diastolic gallop rhythm were present on admission. There was no peripheral edema. Both the venous pressure and the arm-to-tongue circulation time were at the upper limit of normal. Except for a single leukocyte count of 16,000 on admission, there was no leukocytosis. However, a light growth of β-hemolytic streptococci was obtained on throat culture and the antistreptolysin-0 titer was 250 Todd units. The sedimentation rate was elevated, but dropped to normal following the eradication from the throat of β-hemolytic streptococci by penicillin. The serologic test for syphilis was negative. The electrocardiogram showed the changes suggestive of left ventricular disease as previously noted. Cardiac fluoroscopy suggested

great enlargement of the left ventricle and slight enlargement of the right ventricle and the atria. X-ray films of the chest showed marked prominence of the left ventricle (fig. 4). The cardiothoracic ratio was 0.58. He was discharged from the hospital for a period of 2 months with instructions to take 0.1 mg. of digitoxin and 1.0 Gm. of sulfadiazine daily.

He did rather well on restricted activity for some 7 weeks. One day, however, while "on his way downtown," he had a sudden sensation of impending disaster, felt weak, broke out in a sweat, and had to be carried home. The next morning he felt better, but in the afternoon developed weakness, dyspnea, and vomiting. He was at once readmitted to the hospital, where a physical examination showed a rectal temperature of 100 F., a heart rate of 130, and a blood pressure of 94/70. There was marked apprehension, cyanosis, orthopnea, and engorgement of the neck veins. A loud, rough apical systolic murmur transmitted to the posterior axillary line was now present; no other murmurs were noted. The mid-diastolic gallop previously heard over the left ventricle was very prominent. X-ray of the chest showed further cardiac enlargement involving both ventricles. Pulmonary congestion was now evident (fig. 5). There was a slight irregular fever. The leukocyte count increased gradually to 16,000, but the sedimentation rate remained within normal limits. A preparation for L.E. Cells was negative. The antistreptolysin-0 titer was 125 Todd units. The electrocardiogram (fig. 6) showed increased T-wave inversion; however, the patient was receiving digitalis. He failed to improve on a regimen of bed rest, oxygen, digitalis, and mercurial diuretics. On the chance that his heart disease might be the result of rheumatic fever or disseminated arteritis, he was given 300 mg. of hydrocortisone in divided doses with, perhaps, slight improvement for 24 hours. The intensity of the heart failure rapidly increased, however, and he died 10 days after admission. The clinical impression at the time of death was cardiac enlargement due to unknown cause with secondary cardiac insufficiency and congestive failure.

Necropsy

The examination was begun within an hour after death. There was no peripheral edema, and only a negligible amount of free fluid was present in the peritoneal and pleural cavities.

The pericardial sac was greatly enlarged to contain the heart, but the quantity of serous fluid was only slightly in excess of the usual. The heart weighed 640 gm. The serosa was smooth and glistening. There were a number of petechial and ecchymotic hemorrhages in the epicardium, and the subserous fat was rather depleted. All chambers were markedly dilated with fluid blood and postmortem clots. The myocardium was diffusely hypertrophied and of firm consistency. No gross evidence of scarring and no alteration in color were noted. The degree of hypertrophy, somewhat masked by the tremendous dilatation, was suggested by coarseness of the trabeculae carneae and pectinate muscles (fig. 7). The width of the left ventricular wall was not increased; in fact, the apical portion was very thin, as if overstretched.

The mural endocardium was uniformly thin and transparent. The valvular endocardium was delicate and pliable. The mitral ring was dilated to 11.5 cm. and was regarded as relatively insufficient. Other orifices were less dilated and the valves were competent.

The coronary ostia were widely patent. The arteries were balanced and patent throughout, with no appreciable sclerosis. The aorta and its branches showed no constrictions, and there was no gross arteriosclerosis.

Multiple sections representing all areas of the

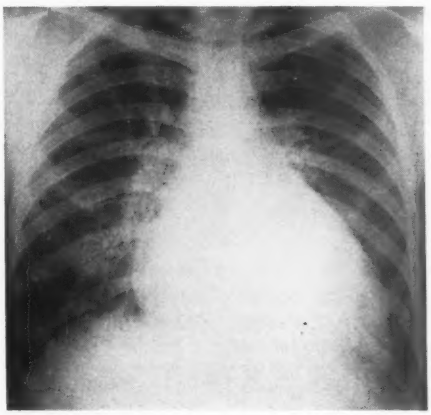

FIG. 5. Chest x-ray on 1/31/55, 9 days before death, Thayer V. A. Hospital, Nashville, Tenn.

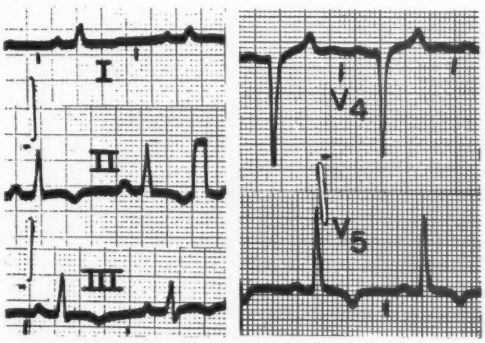

FIG. 6. Electrocardiogram on 2/3/55, 6 days before death, QRS and T-wave changes suggesting left ventricular enlargement and disease.

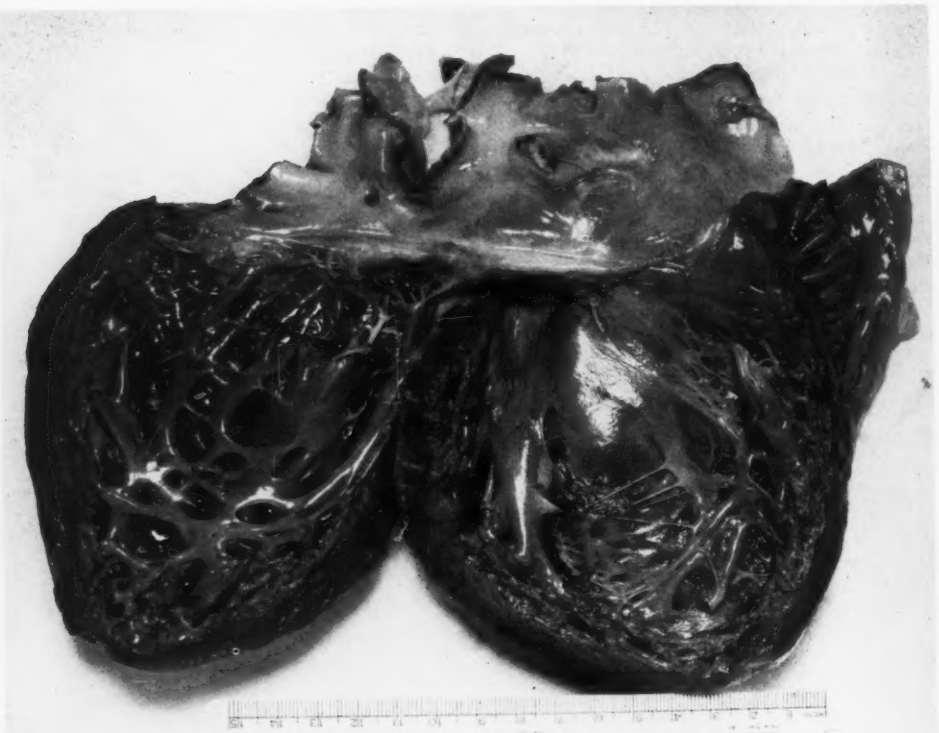

FIG. 7. General topography of the opened left ventricle illustrating its massive dilatation and relative hypertrophy.

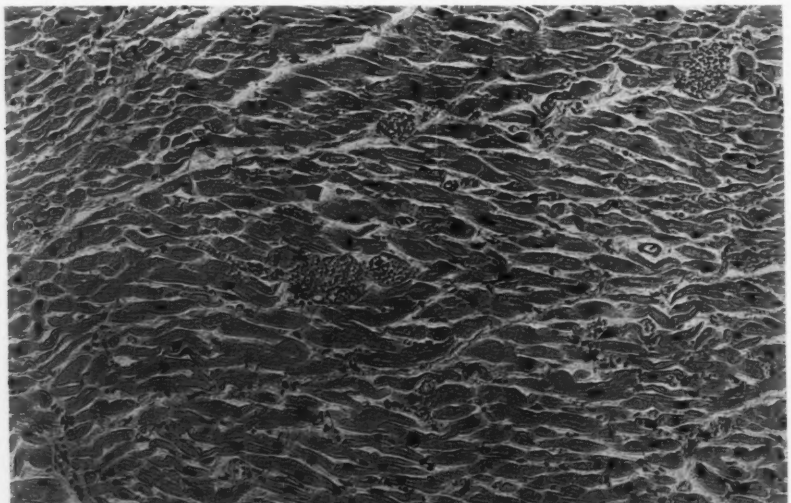

FIG. 8. The ventricular myocardium is hypertrophied but there is no other lesion of note. Hematoxylin and eosin stain. × 100.

heart presented general myocardial hypertrophy. The nuclei were large and frequently angulated (fig. 8). Striations were faint. Some fibers appeared narrow in longitudinal section but the impression was that they were overstretched. There was no necrosis and no scarring. Mild interstitial edema was apparent in some areas and a few lymphocytes and monocytes were encountered near the small vessels. The fibers of the subendocardial layers of the left ventricle often showed unusual paranuclear rarefaction. Glycogen stains (carmine and periodic acid-Schiff) failed to show any excess of carbohydrate.

The major coronary arteries and the aorta presented only slight intimal fibrosis. There was slight epicardial hemorrhage in the areas noted grossly. The venae cavae were normal.

The right lung weighed 830 Gm., and the left weighed 470 Gm. The lower lobes were firm and cyanotic and were of somewhat diminished volume. The upper lobes were reddish-brown in color and of firm consistency. Microscopic sections showed some widening of the alveolar septa and general engorgement of capillaries. In some lobules the alveolar sacs contained protein coagulum and erythrocytes and phagocytes were numerous. Capillary thrombosis and early septal necrosis were evident to some degree in all sections and were very extensive (lobular) in one.

The liver weighed 1770 Gm. and showed passive congestion with central necrosis.

The cortex of the adrenal glands was very narrow and the glomerular zone was severely depleted of lipid. The bone marrow was hyperplastic and the erythrocyte series was predominant. The kidneys showed no lesion of importance.

The principal anatomic diagnoses were idiopathic cardiac hypertrophy and dilatation and acute and chronic passive congestion of the viscera.

Discussion

At the present time one can only speculate whether this type of cardiac enlargement, characterized by progressive congestive failure in the absence of any clearly discernible cause, is the result of a single disease entity. For a discussion of the possibilities, reference is made to the reports on idiopathic cardiac enlargement by Levy,[1-3] Elster,[4] Norris,[5] Kaplan,[6] and Simkins.[7] In our case the cardiac lesions at postmortem examination, aside from hypertrophy and dilatation, were vacuolization of the subendocardial muscle fibers and dilatation of the mitral valve ring. Both these findings seem best explained as the result, rather than the cause, of the heart disease. The patient's fall on board ship may have accelerated his illness, but there was x-ray evidence of increasing left ventricular enlargement prior to his accident. Once present, the relative mitral insufficiency and the cardiac enlargement probably hastened the progress of the congestive failure. The course of the illness suggested a persistent strain upon the left ventricle, but aside from the left ventricular enlargement itself, no clue to the nature of any such burden was evident.

Summary

A case of progressive cardiac enlargement of unknown cause in a 22-year-old man is reported. The patient survived one major bout of congestive failure, but succumbed to a second, 18 months later. Postmortem examination showed only cardiac hypertrophy and dilatation as an explanation for the congestive failure. The difficulty of fitting the facts into the pattern of a single disease entity is discussed and reference made to various earlier studies dealing with the problem.

Acknowledgment

The authors are indebted to Drs. Hugh J. Morgan and Stewart H. Auerbach for criticism of the manuscript and to Mr. Homer Jones and Mrs. Ann Rees for preparation of the illustrations.

Summario in Interlingua

Es reportate un caso de progressive allargamento cardiac in un masculo de 22 annos. Le causa esseva incognoscite. Le patiente superviveva a un major attacco de disfallimento congestive sed succumbeva a un secunde que occurreva 18 menses plus tarde. Le examine post morte revelava solmente hypertrophia e dilatation cardiac como explication possibile del disfallimento congestive. Es discutite le difficultate de combinar le factors in le schema de un specific entitate pathologic. Es citate varie previe studios tractante del mesme problema.

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My truly valuable and respectable friend, Dr. Ash, informed me that Dr. Cawley, then principal of Brazen Nose College, Oxford, has been cured of a Hydrops Pectoris, by an empirical exhibition of the root of the Foxglove, after some of the first physicians of the age had declared they could do no more for him. I was now determined to pursue my former ideas more vigorously than before, but was too well aware of the uncertainty which must attend on the exhibition of the root of a biennial plant, and therefore continued to use the leaves. These I had found to vary much as to dose, at different seasons of the year; but I expected, if gathered always in one condition of the plant, viz, when it was in its flowering state, and carefully dried, that the dose might be ascertained as exactly as that of any other medicine; nor have I been disappointed in this expectation. The more I saw of the great powers of this plant, the more it seemed necessary to bring the doses of it to the greatest possible accuracy. I suspected that this degree of accuracy was not reconcilable with the use of a decoction, as it depended not only upon the care of those who had the preparation of it, but it was easy to conceive from the analogy of another plant of the same natural order, the tobacco, that its active properties might be impaired by long boiling. The decoction was therefore discarded, and the infusion substituted in its place. After this I began to use the leaves in powder, but I still very often prescribe the infusion.—William Withering. *An Account of the Foxglove, and Some of Its Medical Uses.* Birmingham, 1785.

Peripheral Vascular Spasm as a Prodrome of Herpes Zoster

By Leon Blumberg, M.D., and Albert Behrend, M.D.

SEVERE vascular spasm involving the major arteries of an extremity may occur as a result of embolism, inflammation, or local irritation of larger nerve trunks. Recently we were consulted by a patient with severe arterial spasm of one leg. There was no obvious cause for this spasm, and response to conservative therapy was good. Three days after the onset of symptoms, typical lesions of herpes zoster appeared on the affected leg. Review of the literature did not disclose a similar case.

Case Report

Mrs. B. L., a 46-year-old white woman, appeared on September 20, 1955, with a complaint of severe pain in the left thigh and leg brought on by exertion. Pain in the leg was extreme, and movement was barely tolerable. Circulation in the right leg was undisturbed. There was no previous history of cardiac or vascular disease and no history of direct trauma.

On physical examination the left leg was pale, and mottling was beginning to occur below the knee. The leg and foot were cold to touch. The dorsalis pedis and posterior tibial pulses could not be felt, but the left femoral pulse was barely perceptible. The patient was able to move the toes and the extremity, but movement was associated with considerable pain. The pulse rate was 80, and the blood pressure was 144/82. Physical examination was otherwise normal.

Papaverine hydrochloride 60 mg. and tolazoline hydrochloride (Priscoline) 25 mg. were given every 3 hours. Improvement was prompt in response to this therapy. Within 4 hours the mottling had disappeared, and the leg had recovered some color and warmth. The dorsalis pedis and the posterior tibial pulses became faintly perceptible. Pain was also partially relieved. In view of the prompt improvement, hospitalization was not advised. Medication was continued until September 22, when the papaverine was stopped because of vomiting. At this time the leg was warm, and all pulses were present and strong. Pain was still present. On September 23 the typical lesions of herpes zoster appeared on the leg from the inguinal ligament to the sole of the foot, along the distribution of the femoral nerve. The clinical course thereafter was typical of herpes zoster, with a great deal of pain as a dominant feature, relieved only by narcotics. It terminated finally after the patient received radiation therapy.

From the Albert Einstein Medical Center, Philadelphia, Pa.

Discussion

According to Kramer[1] spasm of major peripheral arteries may be induced by various forms of irritation. As an example he mentioned the vascular disturbances seen in patients with cervical ribs. In still other patients, it is impossible to locate the source of irritation. Certain lesions that cause irritation of the larger nerve trunks may also affect peripheral vessels, or the cause may be biochemical or toxic.

Summary

A case of severe vascular spasm involving the major arterial circulation of the lower extremity has been reported. The unusual feature of this case is the fact that the arterial spasm apparently was a prodrome of herpes zoster, the cutaneous manifestations of which appeared 72 hours after the onset of vasospasm. Response of the vasospastic symptoms to nonoperative therapy was good; the herpes zoster required roentgen therapy for relief.

Summario in Interlingua

Es reportate un caso de sever spasmo vascular que involveva le major circulation arterial del extremitate inferior. Le aspecto inusual de iste caso es le facto que le spasmo arterial esseva apparentemente un prodromo de herpes zoster cuje manifestationes cutanee appareva 72 horas post le declaration del vasospasmo. Le responsa del symptomas vasospastic al therapia non-chirurgic esseva bon. Le herpes zoster requireva roentgenotherapia pro su alleviamento.

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Effect of Chlorpromazine on Cerebral Hemodynamics and Cerebral Oxygen Metabolism in Man

By JOHN H. MOYER, M.D., GEORGE MORRIS, M.D., ROBERT PONTIUS, M.D., AND ROBERT HERSHBERGER, M.D.

With the Technical Assistance of C. Polk Smith

Cerebral blood flow frequently decreases following the intravenous administration of chlorpromazine, apparently a result of the reduction in arterial blood pressure. If arterial blood pressure does not decrease, cerebral blood flow is not altered. Chlorpromazine does not exert a depressant effect on cerebral oxygen consumption as morphine does.

CHLORPROMAZINE exerts an inhibitory effect on numerous functions of the central nervous system, particularly on psychomotor and emotional activity. Differing from barbiturates, which have a predominant effect on the cerebrum, chlorpromazine seems to affect primarily the hypothalamic and medullary areas of the brain.[1] It acts without producing the same degree of somnolence that barbiturates and opiates do. Since opiates and barbiturates depress cerebral oxygen uptake[2] without affecting cerebral blood flow, it was decided to do similar studies before and after the administration of chlorpromazine in order to compare the response in normal control subjects.

METHODS AND MATERIALS

Thirteen normotensive control subjects were studied. Nine of these received the chlorpromazine intravenously and 4 received it intramuscularly. The latter 4 subjects were selected because of the rather marked hypotensive responses observed after intravenous administration of the drug which in itself may reduce cerebral blood flow.[3] Following intramuscular administration of chlorpromazine, the hypotensive effect was less marked than after intravenous administration. Therefore it was reasoned that the effects of blood pressure alterations due to chlorpromazine could be at least partially circumvented by giving the drug intramuscularly.

The subjects were studied in a fasting state in the supine position. Measurements of the pulse rate, respiratory rate, and blood pressure were taken during a control period and repeatedly during the course of each experiment. Arterial blood pressure was recorded by direct intra-arterial manometry. Cerebral blood flow was determined by the nitrous oxide method of Kety and Schmidt.[4] Following the control observations, 50 mg. of chlorpromazine were given intravenously (over a 10-minute period of time) to 7 subjects and intramuscularly to 4 subjects. Two additional subjects received 25 mg. and 60 mg., respectively, by the intravenous route. A second cerebral blood flow determination was made 1 hour after the administration of the drug. The blood pH determinations were done on a Beckman pH meter with a water bath maintained at body temperature. The Van Slyke nomogram was used to estimate CO_2 tension (PCO_2). Cerebral oxygen consumption ($CMRO_2$) and cerebral vascular resistance (CVR) were calculated as previously described.[4,5] The Van Slyke manometric apparatus was used for the gas analysis, and aerosol was used as the hemolytic agent.

RESULTS

The effects of chlorpromazine (Thorazine)* on cerebral blood flow, mean blood pressure and cerebral oxygen metabolism are recorded in table 1. Chlorpromazine usually produced a temporary increase in respiratory rate follow-

From the Departments of Medicine, Surgery, and Pharmacology, Baylor University College of Medicine, Houston, Tex.

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* Furnished by Smith, Kline & French Laboratories.

TABLE 1.—*Cerebral Hemodynamic Response to Chlorpromazine (SKF 2601)*

Patient	Mean blood pressure		Cerebral blood flow, ml./100 Gm./min.		Cerebrovascular resistance		Cerebral Oxygen uptake*		Dose† mg.	Per cent oxygen saturation			
										Arterial		Venous	
	C	D	C	D	C	D	C	D		C	D	C	D
Group A													
1. V.G.	81	69	46	51	1.8	1.4	2.1	2.9	50	92	92	65	55
2. A.B.	101	70	40	29	2.5	2.4	3.5	3.4	50	94	97	50	38
3. E.L.	103	82	43	35	2.4	2.3	3.6	3.9	50	94	98	50	40
4. O.A.	81	76	44	48	1.8	1.6	2.4	2.5	50	99	94	67	62
5. N.N.	103	116	65	56	1.6	2.1	4.6	3.4	25	98	96	57	62
6. C.P.	107	86	61	36	1.8	2.4	1.9	2.2	60	92	92	73	54
7. F.R.	94	87	38	42	2.5	2.1	4.1	3.9	50	99	95	46	49
8. F.S.	85	63	54	33	1.6	1.9	2.9	1.7	50	93	91	55	58
9. A.S.	101	76	37	38	2.7	2.0	3.3	3.7	50	91	91	47	42
Mean	95	81	48	41	2.1	2.0	3.2	3.1	48	95	94	57	51
% of Control		85		85		95		97			99		89
p Value‡		<.01		<.10		<.50		<.50			<.40		<.10
Group B													
10. A.L.	78	80	45	45	1.7	1.8	2.8	3.0	50	96	98	59	59
11. E.M.	95	101	35	41	2.7	2.5	2.0	2.5	50	95	88	61	52
12. G.F.	96	92	58	60	1.7	1.5	3.5	3.8	50	97	99	65	66
13. R.T.	98	89	59	54	1.7	1.6	3.0	2.5	50	98	97	67	69
Mean	92	91	49	50	2.0	1.9	2.8	3.0	50	97	96	63	62
% of Control		99		102		95		107			99		98

Group A, intravenous administration.
Group B, intramuscular administration.
C = Control observations
D = Observations 1 hour after the administration of chlorpromazine
* = ml./100 Gm. of brain/min.
† = Dose chlorpromazine
‡ = Statistical analysis by R. A. Seibert: $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$

ing the intravenous administration of the drug, but, by the time studies of the post drug cerebral blood flow were done, the respiratory rate and depth were similar to the control observations. Also, the pulse rate increased rather significantly immediately after the chlorpromazine administration, but this effect was usually insignificant after 1 hour; however, a moderate increase in pulse rate was sometimes observed at the time of the second determination of cerebral blood flow. The subjects universally showed less apprehension after the administration of chlorpromazine, but only 2 of them (N.N. and F.S.) showed a noticeable degree of somnolence.

There was a reduction in mean blood pressure in all but 1 subject following intravenous administration of the drug ($p < 0.01$). This drop persisted throughout the period of the experiment and usually was evident for 2 or 3 hours. Associated with the reduction in mean blood pressure there was frequently a slight reduction in cerebral blood flow. However, this was a variable response and was not consistent enough to be statistically significant ($p < 0.10$) for the number of subjects* studied. Whenever a marked reduction in cerebral blood flow occurred, it was preceded by an acute reduction in mean blood

* If a larger group of patients had been studied, this value probably would have become statistically significant.

TABLE 2.—*Effect of Chlorpromazine on Cerebral Blood Oxygen and Carbon Dioxide*

Patient	Age	Sex	Arterial O_2 Volume %		Venous O_2 Volume %		Arterio-venous O_2 Volume %		Arterial CO_2 Volume %		Venous CO_2 Volume %		Arterial PCO_2		Venous PCO_2		Hematocrit	
			C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Group A																		
1. V.G.	24	♂	14.0	14.0	9.4	8.4	4.6	5.6	48.5	52.2	53.7	56.5	45	48	55	58	38	39
2. A.B.	34	♂	18.6	19.3	9.8	7.5	8.8	11.8	43.8	43.6	50.6	53.3	41	43	52	45	47	47
3. E.L.	38	♂	18.3	19.0	9.9	7.9	8.4	11.1	38.4	37.3	46.2	46.6	38	35	45	47	45	47
4. O.A.	21	♂	16.4	15.4	11.0	10.1	5.4	5.3	47.5	50.8	51.5	55.9	44	44	57	50	41	37
5. N.N.	40	♂	16.9	16.6	9.8	10.6	7.1	6.0	38.3	45.1	45.5	50.5	—	—	—	—	44	43
6. C.P.	30	♂	14.7	14.7	11.6	8.6	3.1	6.1	50.2	49.8	53.7	53.8	44	39	49	53	39	36
7. F.R.	37	♂	20.2	19.5	9.5	10.1	10.7	9.4	43.8	47.0	55.0	55.3	38	40	43	56	52	50
8. F.S.	28	♂	16.1	15.6	10.8	10.3	5.3	5.3	49.5	51.3	55.7	56.3	46	51	56	56	41	39
9. A.S.	35	♂	18.1	18.1	9.3	8.4	8.8	9.7	43.9	45.6	51.4	53.6	46	45	52	52	47	47
Mean			17.0	16.9	10.1	9.1	6.9	7.8	44.9	47.0	51.5	53.5	43	43	51	52	44	43
% of Control				99		90		113		105		104		100		102		98
p Value				<.50		<.05		<.10		<.50		<.01		<.50		<.50		<.20
Group B																		
10. A.L.	30	♂	16.7	17.1	10.4	10.4	6.3	6.7	42.0	42.3	50.4	49.6	37	37	46	48	46	46
11. E.M.	46	♀	16.2	15.0	10.4	8.9	5.8	6.1	42.0	40.0	47.5	47.5	36	32	44	42	44	43
12. G.F.	27	♀	18.3	18.7	12.2	12.4	6.1	6.3	39.6	41.2	45.0	47.2	39	40	48	50	42	45
13. R.T.	38	♀	15.7	15.6	10.7	11.0	5.0	4.6	46.0	48.1	42.0	43.1	42	44	47	49	46	46
Mean			16.7	16.6	10.9	10.7	5.8	5.9	42.4	42.9	46.2	46.9	39	38	46	47	45	45
% of Control				99		98		102		101		102		97		102		100

Group A, intravenous administration.
Group B, intramuscular administration.
C = Control observations
D = Observations made 1 hour after the administration of chlorpromazine.

pressure. The relationship between blood pressure reduction and decreased cerebral blood flow was confirmed by the observations made on the 4 subjects who received the drug intramuscularly, since neither mean blood pressure nor cerebral blood flow decreased in this group.

Despite the slight reduction in cerebral blood flow that was frequently observed following the administration of chlorpromazine intravenously, it was not associated with a reduction in cerebral oxygen uptake ($p > 0.50$). The mean cerebral oxygen uptake prior to chlorpromazine administration was 3.2 ml./100 Gm. of brain/min. and after drug administration it was 3.1 ml./100 Gm. of brain/min. (97 per cent of control), indicating that cerebral oxygen metabolism was not affected by the administration of chlorpromazine. When the drug was given by the intramuscular route, there was likewise no effect on cerebral oxygen uptake.

Among the significant effects on blood gases was a rather consistent reduction in jugular blood oxygen content ($p < 0.05$) following intravenous administration of chlorpromazine. This change was frequently associated with an increase in arterial-venous oxygen difference ($p < 0.10$), probably a reflection of the occasional reduction in cerebral blood flow associated with the mild hypotensive response to chlorpromazine administered intravenously. When the drug was given intramuscularly and the hypotensive effect did not occur, neither the oxygen content of the jugular blood nor the cerebral arterial-venous oxygen difference was affected (table 2).

As the oxygen content of the jugular blood decreased following intravenous administration of chlorpromazine, there was a slight increase

in venous CO_2 content ($p < 0.01$) but not in pCO_2. Again, this increase occurred only after intravenous administration and probably reflects the frequent reduction in cerebral blood flow associated with the hypotensive response to the drug. After intramuscular administration there was no significant effect on CO_2 content of the blood, coming from or going to the brain.

Discussion

It appears that chlorpromazine has very little direct effect on cerebral blood flow or cerebral oxygen metabolism per se, and the only alterations that occur are those that follow the reduction in blood pressure resulting from the peripheral adrenergic blocking effect of the drug.[1] Figure 1 summarizes a typical response. The reduction in mean blood pressure may or may not be accompanied by a concurrent reduction in cerebral blood flow (table 1). This cerebral hemodynamic response is no different from that observed when other hypotensive agents, such as ganglionic and adrenergic-blocking agents, are given to normotensive individuals and the blood pressure is reduced to hypotensive levels.[3, 6] For example, in figure 2 is seen the typical hemodynamic response of a normotensive individual given a continuous infusion of hexamethonium.[6] As the blood pressure decreases to hypotensive levels, cerebral blood flow is reduced concurrently. This change is associated with an increase in the cerebral arteriovenous oxygen difference and a minimal, or no, alteration in oxygen uptake by the brain.

Further support to the blood pressure effect on cerebral blood flow was furnished when the chlorpromazine was given intramuscularly. Under these circumstances the sharp reduction in mean blood pressure was not observed with the subject in the supine position (as was the case in the current experiment). As a result, cerebral blood flow was not reduced and cerebral arteriovenous oxygen difference was not affected. Furthermore, in those subjects whose reduction in cerebral blood flow was associated with a hypotensive response to intravenously administered chlorpromazine, intravenous infusion of norepinephrine brought about a return toward normal in cerebral blood flow (figs. 1 and 3), as the mean blood pressure increased to the control levels. There was no effect on cerebral arteriovenous oxygen difference and no effect on cerebral oxygen uptake (fig. 1) during the infusion of nor-

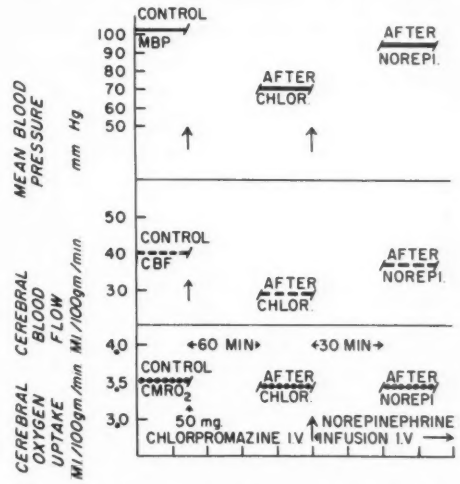

FIG. 1. Response to chlorpromazine given intravenously. As the blood pressure decreased, cerebral blood flow decreased without affecting cerebral oxygen uptake. When the arterial blood pressure was then increased with an infusion of norepinephrine, cerebral blood flow also increased.

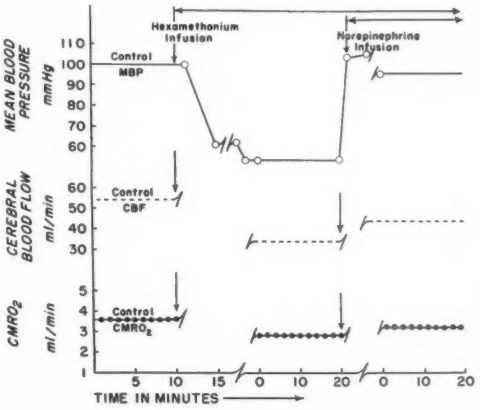

FIG. 2. Typical cerebral hemodynamic response to blood pressure reduction employing a continuous infusion of a ganglionic-blocking agent. As the blood pressure decreases, cerebral blood flow is depressed. Cerebral oxygen uptake is not altered unless the reduction in cerebral blood flow becomes marked.

epinephrine if these had not previously been altered by the hypotension associated with chlorpromazine administration. Occasionally a slight depression in cerebral oxygen consumption accompanied the reduction in cerebral blood flow associated with the hypotension due to chlorpromazine administered intravenously. This was an erratic response and was apparently due to insufficient oxygen being extracted from the blood flowing through the brain to compensate for the degree of reduction in cerebral blood flow that accompanied the hypotension. When the blood pressure was returned to control levels in these patients by the infusion of norepinephrine, cerebral oxygen consumption, as well as cerebral blood flow, increased toward normal. Such an example is presented in subject F.S., in whom the reduction in cerebral blood flow was associated with a depression in cerebral oxygen consumption (fig. 3). Both alterations were corrected by increasing the blood pressure to control values with the continuous intravenous infusion of norepinephrine. Similar results were achieved by giving norepinephrine to subjects 2 (A.B.), 6 (C.P.), and 8 (F.S.), who showed a reduction in cerebral blood flow following the administration of chlorpromazine, (figs. 1 and 3). Doses of chlorpromazine up to 300 mg. appear to produce no difference in response from that noted in the current study.[7]

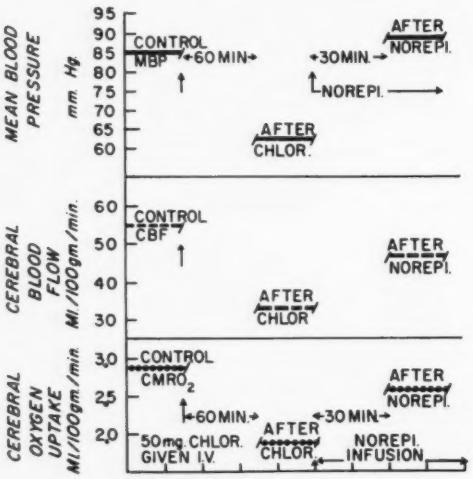

FIG. 3. Response to chlorpromazine given intravenously in a subject who showed a marked reduction in mean blood pressure and cerebral blood flow. The increased extraction of oxygen from the cerebral blood was inadequate to prevent a reduction in cerebral oxygen uptake. When the blood pressure was increased to control levels with norepinephrine both cerebral blood flow and cerebral oxygen uptake increased.

The metabolic effect of chlorpromazine is quite different from that observed with barbiturates and morphine.[2] For example, figure 4 presents a typical response to 60 mg. of morphine given intravenously. The morphine did not affect cerebral blood flow, but did cause a marked reduction in cerebral oxygen uptake. Apparently this results from a general depressant effect on cerebral metabolism. Similar observations have been made following the administration of intravenous pentothal.[2]

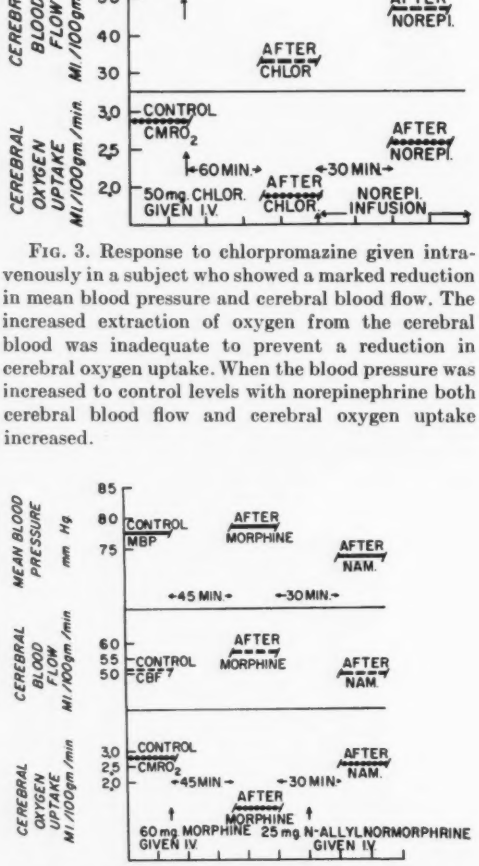

FIG. 4. Cerebral response to morphine given intravenously. Cerebral oxygen uptake was depressed without affecting mean blood pressure or cerebral blood flow. The process was reversed with N-allylnormorphine [Nalline (NAM)].

SUMMARY

The cerebral hemodynamic effects of chlorpromazine administered intravenously and intramuscularly were observed in 13 subjects. Cerebral blood flow was frequently reduced following the intravenous administration of chlorpromazine, but apparently this change was a result of the associated reduction in mean arterial blood pressure, rather than a direct effect of the drug on the cerebral circulation. When the blood pressure was then

elevated to normotensive levels with norepinephrine, the cerebral blood flow returned toward normal. Chlorpromazine did not exert a direct depressant effect on cerebral oxygen consumption. When chlorpromazine was given by the intramuscular route, the blood pressure was not reduced significantly, and cerebral blood flow and cerebral oxygen consumption were not altered. The metabolic effect of chlorpromazine is quite different from that of morphine and barbiturates, since the latter agents depress cerebral oxygen uptake without affecting cerebral blood flow.

Summario in Interlingua

Esseva observate in 13 subjectos le effectos cerebro-hemodynamic de chlorpromazina in administrationes intravenose e intramuscular. Le fluxo de sanguine cerebral esseva frequentemente reducite post le administration intravenose de chlorpromazina, sed il pare que iste alteration esseva le resultato del associate reduction del median pression arterial plus tosto que un effecto directe exercite per le droga super le circulation cerebral. Le re-elevation del pression sanguinee a nivellos de normotensivitate effectuate per medio de norepinephrina esseva sequite per le renormalisation del fluxo de sanguine cerebral. Chlorpromazina non exerceva un effecto directemente depressive super le consumption cerebral de oxygeno. Quando chlorpromazina esseva administrate intramuscularmente, le pression sanguinee non se reduceva significativemente, e le fluxo de sanguine cerebral e le consumption cerebral de oxygeno non esseva alterate. Le effecto metabolic de chlorpromazina es multo differente ab le effecto de morphina e del barbituratos que deprime le acceptation cerebral de oxygeno sin afficer le fluxo de sanguine cerebral.

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Angioscopic Changes in the Smaller Blood Vessels in Diabetes Mellitus and their Relationship to Aging

By JØRN DITZEL, M.D.

Observations with the stereoscopic dissecting microscope of the bulbar conjunctiva disclose vascular changes before pathologic changes are seen with the ophthalmoscope. In diabetic subjects lesions concomitant with aging are accelerated and, in addition, specific abnormalities characteristic of diabetes are observed.

UNTIL recently the vascular lesions in diabetes mellitus have been considered "arteriosclerotic" in origin. It was said that the high incidence of malignant vascular disease was due to an accelerating effect of diabetes upon the development of arteriosclerosis and normal aging.[1, 2]

Lately, there has been a change in opinion on this point and more investigators now regard the diabetic vascular syndrome as a specific entity characteristic of the disease.[3, 4] This belief is mostly based on the fact that diabetic retinopathy and intercapillary glomerulosclerosis, both involving small blood vessels, show some characteristic morphologic features easily distinguishable from those of arteriosclerosis.[5, 6] Evidence at present suggests that the diabetic lesions in the retina and the kidney are various manifestations of one *generalized*, slowly developing disease in the smaller blood vessels (diabetic microangiopathy). The increased fragility of the small blood vessels in the subcutaneous tissue of long-term diabetic subjects indicates the extensiveness of this microangiopathy.[7, 8]

Further information as to the nature of these changes can be obtained by studying other vascular beds of diabetic subjects. The bulbar conjunctiva offers unique possibilities for direct biomicroscopic observations of the smaller blood vessels and the circulating blood.[9] These vessels can reasonably be considered representative of those of the subcutaneous tissue, since the 2 areas are closely related embryologically and anatomically.

The purpose of the present investigation was to evaluate the morphologic and hemodynamic changes occurring in the conjunctival vascular bed of diabetic and "healthy" subjects of various ages in order to determine whether changes in the diabetics differ from those occurring with normal aging.

METHODS AND MATERIAL

The material was obtained from observations of 220 diabetic and 175 "healthy" subjects, chosen with the object of providing an approximately even sex distribution in 4 convenient age groups: group 1, children, ages 4 to 15; group 2, young adults, ages 16 to 35; group 3, middle age, ages 36 to 55; and group 4, old age, ages 56 to 75.

The selected diabetic and control subjects formed comparable age and sex groups. The data on the number, sex, age, duration of diabetes, incidence of retinopathy, and insulin dose are given in table 1. The observer was unaware of the diagnosis and of the medical history of the subjects, since the selection of both diabetic and nondiabetic individuals was made by a cooperating investigator. The single exception was in the case of the children in whom the presence or absence of diabetes was known, but no other details of the medical history or chronologic age, etc., were revealed to the observer. Excluded from the study were all individuals who suffered from conditions that might cause interfering changes in the vascular bed: local infection or irritation, allergies, congestive heart failure, or infections. Furthermore, all diabetic subjects had normal blood pressure, defined in the present work as a systolic pressure below 150 and a diastolic below 100. They all were receiving insulin daily and all were in a state of fairly good control at the time

From the Baker Clinic Research Laboratory, New England Deaconess Hospital and the Joslin Clinic, Boston.

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TABLE 1.—*Pertinent Data on All Individuals Investigated*

Group	Sex	Number	Age Range (*years*)	Average Age (*years*) mean ± s.d.	Duration of Diabetes (*years*) mean ± s.d.	Incidence of Retinopathy	Insulin Dose (internat. units) mean
Diabetic Subjects							
Children	M	35	4–15	11.3 ± 3.3	5.6 ± 3.4	1	42
	F	35		10.7 ± 2.6	4.3 ± 2.7	0	47
Young adults	M	25	16–35	26.3 ± 6.3	11.4 ± 7.8	7	62
	F	25		26.4 ± 6.1	10.2 ± 8.5	8	46
Middle age	M	25	36–55	48.0 ± 4.9	11.1 ± 8.6	8	32
	F	25		46.4 ± 6.3	10.5 ± 8.9	8	37
Old age	M	25	56–75	61.4 ± 4.2	6.8 ± 4.2	4	21
	F	25		63.5 ± 5.7	11.2 ± 8.0	5	24
Control Subjects							
Children	M	56	4–15	10.6 ± 3.8			
	F	29		9.7 ± 3.3			
Young adults	M	15	16–35	27.8 ± 3.7			
	F	15		24.3 ± 5.4			
Middle age	M	15	36–55	47.0 ± 6.6			
	F	15		44.3 ± 4.5			
Old age	M	15	56–75	63.6 ± 5.1			
	F	15		61.8 ± 6.4			

of the examination, i.e., none had acidosis. The groups are approximately comparable as to duration of diabetes and insulin dose except for the children, who obviously had to have a lesser duration of the disease. Only 41 diabetics showed any retinopathy and these individuals were distributed rather generally throughout the groups.

The subjects were placed in the supine position while the observations were being made. The stereobinocular microscope of the Grenough type (Leitz) was used to examine the lateral part of the bulbar conjunctiva of each eye. Normally the observations were made with a magnification of 48× or 64×. The use of the Shahan ophthalmic lamp provided maximal illumination with negligible production of heat. A further detailed description of this method is given by Bloch.[9]

Immediately after each observation, information concerning vascular, perivascular, and intravascular changes was recorded. Dynamic alterations in the tone of the minute vessels were evaluated from the ratio between the diameter of the arterioles and the accompanying larger venules at various sites. Morphologic vascular changes were assessed from configuration of the arterioles, the capillaries, and the venules. These changes included irregularities, sacculations, and tortuosities.* Perivascular changes were indicated by the presence of edema, localized or diffuse "hyaline" infiltration, and hemorrhages or pigment from old hemorrhages in the conjunctival tissue. Intravascular changes were based on a description of the hemodynamics in different parts of the vascular compartment. This included grading of the degree of aggregation of the red blood cells.

Examples of the observed changes were photographed by a specially developed technic.[10]

RESULTS

Table 2 illustrates the results of the study in the diabetic as compared to the control subjects according to vascular and perivascular changes observed in the conjunctival vascular bed.* Separate analysis of the findings has been made to evaluate the influence of age upon the vascular bed in the "healthy" and in the diabetic subjects. A comparison was also made between the significant† changes in the diabetic

* A localized widening of a vessel exceeding its double diameter is called a sacculation; a smaller widening is called a dilatation. A distention is a uniform increase in the diameter of a vessel. A microaneurysm is defined as a globular capillary sacculation, with visible afferent and efferent vessels.

* No distinction has been made for sex in the figures quoted, since no significant differences were found. The small figures in the lower right-hand corner in table 2 indicate the incidence of the changes in the control subjects.

† Unless otherwise indicated, whenever the terms "significant" or "statistically significant" are used throughout the paper, the significance has been calculated from the standard error of the difference, which equals: $\frac{pq}{n_1} + \frac{pq}{n_2}$. If the difference between the 2 observed percentages is 3 or more times the standard error of the difference, the 2 groups have been considered significantly different ($p < 0.01$).

and in the control subjects in order to determine the effect of diabetes alone upon the vascular bed exclusive of the aging process.

Vascular Changes

Arterioles. Jagged irregularities in the configuration of the terminal arterioles were occasionally observed in both diabetic and nondiabetic subjects. The number of nondiabetic cases that showed this lesion was small, and the incidence was only significantly correlated to age when the individuals in the 2 younger groups were compared with the 2 older groups. As may also be seen from table 2, the incidence of this lesion in the diabetic groups increased significantly with increasing age ($\chi^2 = 25.01$, $p < 0.01$, $n = 3$). When compared with their controls, the diabetic subjects showed a higher incidence of arteriolar lesions, which was, however, significant only in the old subjects (group 4). It therefore may be concluded that the lesion in the terminal arterioles is an aging change, and diabetes may possibly accelerate it.

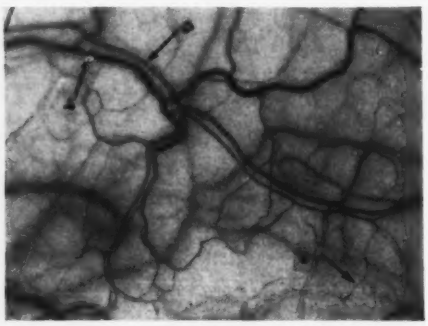

FIG. 1. The conjunctival vascular bed of a "healthy" child (14 years). Characteristics: (1) the smaller blood vessels show regular configuration (*a:* arteriole, *c:* capillary, *v:* venule); (2) no intravascular erythrocyte aggregation; (3) no edema. 48×.

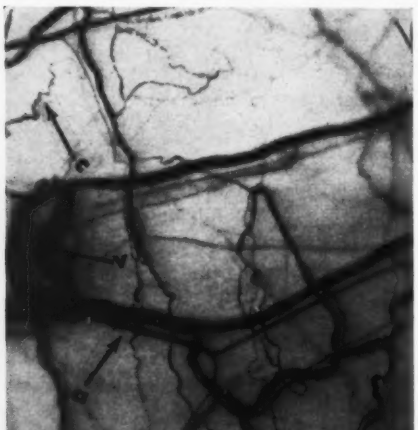

FIG. 2. The conjunctival vascular bed of a young diabetic patient (21 years) shows angular elongation of the venous part of the capillaries (*c*) and elongation and distention of the venules (*v*). 48×.

Capillaries. The capillaries in the bulbar conjunctiva of the "healthy" subjects for the most part followed a smooth course (fig. 1). However, capillary elongation, appearing in the venous part as mixed angularities and tortuosities, was often encountered among the young diabetic subjects (group 1, 76 per cent; group 2, 72 per cent) but significantly less frequently in the older age groups (groups 3 and 4, 30 per cent) (fig. 2). When compared to the incidence in the control subjects, approximately 10 per cent, this capillary anomaly was found to be highly characteristic ($p < 0.01$) of the *young* diabetic subjects, while the difference in incidence in the older diabetic persons just reached the limit of significance. Consequently, this capillary change is not due to aging, but is a characteristic feature of diabetes, particularly in those individuals with onset of the disease early in life.

Venules. The venular changes (fig. 3) were categorized in 3 ways: venular irregularities, venular sacculations, and arteriolar-venular ratio.

Wavy and jagged venular irregularites occurred in the smaller venules (12–60 microns) of both nondiabetic and diabetic subjects. The incidence of this irregularity increased significantly with age in both the nondiabetic ($\chi^2 = 55.56$, $p < 0.01$, $n = 3$) and in the diabetic subjects ($\chi^2 = 26.00$, $p < 0.01$, $n = 3$). The incidence of venular irregularities was significantly higher in the diabetic than in the nondiabetic subjects in the 3 younger age groups. Thus the per cent of this change appearing in the conjunctiva of the diabetic children (group 1) was approximately equal to the non-

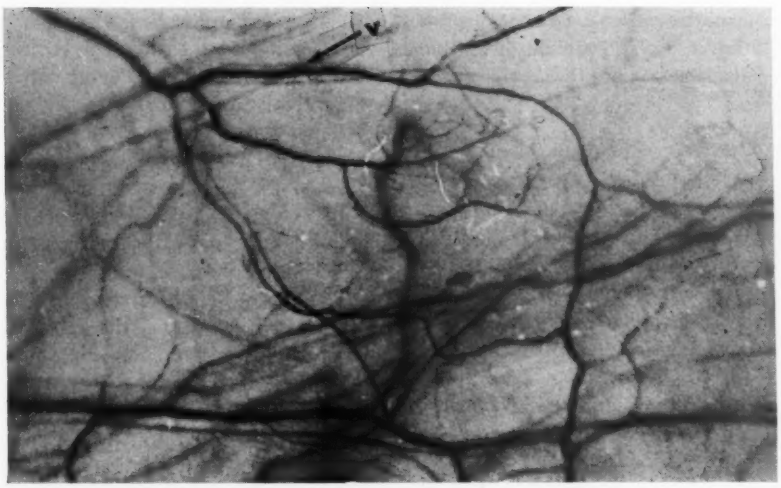

FIG. 3. The conjunctival vascular bed of a "healthy" adult (52 years) shows an irregular network and numerous venular irregularities (*v*). 48×.

TABLE 2.—*The Degree of Vascular and Perivascular Changes in the Bulbar Conjunctiva Correlated to Age in Diabetic Subjects*

	GROUP I TO CHILDREN 4–15 YEARS	GROUP II 50 YOUNG 16–35 YEARS	GROUP III SOMIDDLE AGE 36–55 YEARS	GROUP IV SO OLD AGE 56–75 YEARS
ARTERIOLAR IRREGULARITIES	3% (0%)	8% (3%)	18% (19%)	34% (13%)
CAPILLARY ELONGATION	76% (7%)	72% (10%)	30% (10%)	30% (0%)
VENULAR IRREGULARITIES	50% (12%)	68% (17%)	86% (57%)	84% (77%)
VENULAR SACCULATIONS	8% (0%)	16% (7%)	46% (17%)	36% (27%)
ARTERIOLAR/VENULAR DIAMETER A/V RATIO<1:3	47% (2%)	48% (0%)	28% (0%)	6% (0%)
EDEMA	57% (4%)	40% (3%)	10% (0%)	10% (0%)
"HYALINE" INFILTRATION	16% (0%)	62% (7%)	60% (33%)	74% (37%)
HEMORRHAGES	2% (0%)	24% (3%)	34% (7%)	29% (7%)

The small figures in the lower right-hand corner indicate the incidence of the changes in the control subjects.

diabetic members of group 3. Venular irregularities seem, therefore, to be part of the normal aging process and to be accelerated by diabetes.

Venular sacculations were observed in the larger venules measuring 60 microns or more in diameter. The data given in table 2 show that this lesion occurred less frequently than the smaller irregularities. However, a significant increase in incidence occurred commensurate with age in both nondiabetic ($\chi^2 = 19.71$, $p < 0.01$, $n = 1$) and in diabetic individuals ($\chi^2 = 26.30$, $p < 0.01$, $n = 3$). There was a significantly higher incidence of venular sacculation among the diabetic groups than in the nondiabetic groups and thus this venular change seems also to be accelerated by diabetes.

In order to evaluate dynamic changes occurring in the tone of the arterioles and venules the average A/V ratio was estimated. This ratio was determined by measurements of the diameter of the arterioles and accompanying larger venules. It was found that this ratio was 1:3 to 1:2 in all but 1 of the "healthy" subjects. In many diabetic subjects the larger venules showed marked distention, elongation, and congestion, and this change was often accompanied by a slight constriction of the accompanying arteriole. The A/V ratio in diabetic persons was found to reach values as low as 1:10. The change in the A/V ratio was particularly notable in the 2 younger groups (group 1, 47 per cent; group 2, 48 per cent) while less so in the older age groups (group 3, 28 per cent; group 4, 6 per cent). A χ^2 test indicated that this change, like capillary elonga-

tion, was inversely correlated with age ($\chi^2 = 28.21$, $p < 0.01$, $n = 3$). The venular distention and arteriolar constriction are *highly* characteristic of diabetes.

Perivascular Changes

The perivascular changes appear to be related to leakage of plasma and red blood cells through the walls of the venous part of the capillaries and the smaller venules.

Edema. Edema was encountered in only 4 cases among the "healthy" subjects and can be regarded as being inconsistent with good health and a normal functioning vascular bed. Microscopic and occasionally macroscopic edema of the conjunctival tissue was, however, often found in the younger diabetic subjects (group 1, 57 per cent; group 2, 40 per cent) while the occurrence of this change in the diabetic persons above the age of 35 was significantly less frequent (group 3, 10 per cent; group 4, 10 per cent; $\chi^2 = 44.03$, $p < 0.01$, $n = 3$). The edema appeared to be closely related to the presence of venular distention. Both these changes were present in many young diabetic persons without any evidence of retinopathy and nephropathy.

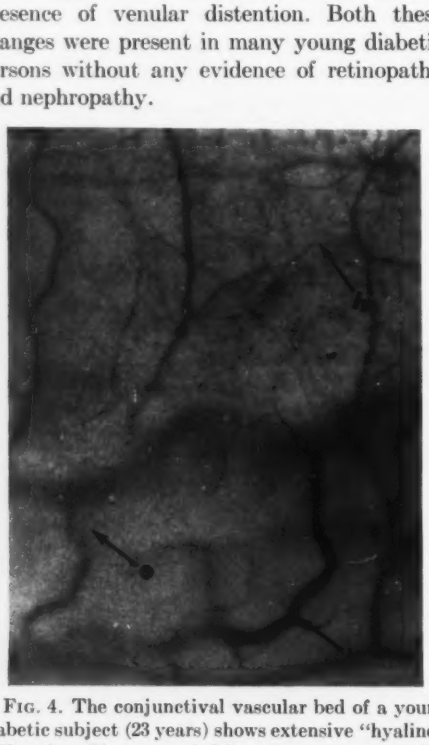

FIG. 4. The conjunctival vascular bed of a young diabetic subject (23 years) shows extensive "hyaline" infiltration (*h*) surrounded by edema (*e*) and a distended venule (*v*). 64×.

"Hyaline" infiltration. "Hyaline" infiltration is a common and easily observed senile change in the bulbar conjunctiva. In the nondiabetic individuals it appeared as a grayish or slightly yellowish spot in the perivascular tissue and was situated some distance from the limbus. This change was not found among the children and in only 2 cases (7 per cent) among the young adults, while its occurrence in the subjects above the age of 35 was significantly higher (group 3, 33 per cent; group 4, 37 per cent). In the young diabetic patients the "hyaline" infiltration appeared microscopically somewhat different from that of the nondiabetic subjects, but it appeared to be similar in the older diabetic and nondiabetic individuals. The "hyaline" infiltration in the young diabetic patients was extensive, cotton-wool-like, and diffuse (fig. 4). The incidence of "hyaline" infiltration was high in all 3 diabetic groups above the age of 15 (group 2, 62 per cent; group 3, 60 per cent; group 4, 74 per cent), while only 16 per cent of the children showed this tissue change. There appeared to be an abrupt rise in incidence at the age of approximately 25. When the incidence of the change was compared in the diabetic and the nondiabetic subjects, there was a markedly significant difference in all age groups. It therefore appears that even though the "hyaline" infiltration of the conjunctival tissue may be related to aging, the presence of diabetes has a markedly accelerating effect upon its formation.

Hemorrhages. Small blotchy hemorrhages or pigment of old hemorrhages was seen in approximately the same number of cases among the 3 older groups of diabetic subjects (group 2, 24 per cent; group 3, 34 per cent; and group 4, 29 per cent), while it was only observed in 1 case among the diabetic children. There was a significantly higher incidence of small hemorrhages among the diabetic than the nondiabetic subjects. It appears therefore that diabetes has an accelerating effect on the formation of hemorrhages in the conjunctiva.

Over-all Vascular and Perivascular Changes

In order to give an over-all picture of the relationship between age and the degree of vascular and perivascular damage in the nondiabetic individuals, the findings were graded

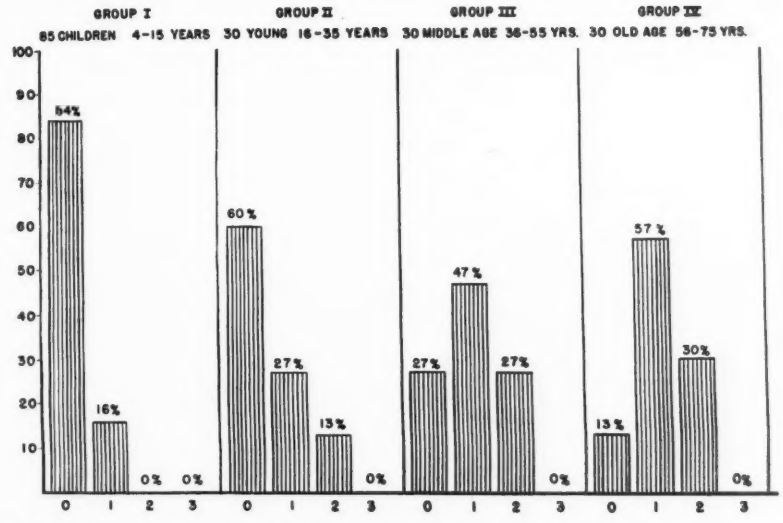

FIG. 5. The degree of vascular and perivascular changes in the bulbar conjunctiva correlated to age in "healthy" subjects.

according to an arbitrary scale that has been used before[11] (fig. 5). With an increase in years, there appear progressively more changes in the vascular bed. A χ^2 test demonstrated that this relationship was statistically significant ($\chi^2 = 63.98$, $p < 0.01$, $n = 9$). None of the subjects fall into grade 3 because this combination of changes has not been found in healthy nondiabetic individuals.

No single grading system of the over-all vascular and perivascular changes can be employed in discussing the vascular pathology in diabetic individuals of various ages because different lesions appear in the smaller blood vessels, depending upon the age at onset of diabetes. Although a grading system cannot be used, all the single features such as arteriolar and venular irregularities characteristic of normal aging were found significantly more frequently in the diabetic than in the control subjects, as was shown above. Each group of diabetic subjects also showed, besides normal aging changes, alterations more characteristic of the diabetes itself, and these latter alterations are most obvious in the "juvenile" diabetic individuals with onset prior to ages 20 to 25.

Since the anomalies such as capillary elongation characteristic of diabetes are most obvious in the younger age groups, an evaluation of the effect of the duration of diabetes upon the vascular bed is also inaccurate if diabetic persons of various ages (4 to 75 years) are grouped together. An analysis made of the data from the children only (group 1) established that the degree of vascular change was positively correlated to the duration of the disease.[12]

Intravascular Changes

The most easily recognizable intravascular change is the aggregation of red blood cells associated with slowing of blood flow. In order to take into consideration the size, placement, and physical properties of these aggregates, a grading system was used:

0 = Completely unaggregated blood stream.
1 = Small aggregates in the smaller venules.
2 = Consistent aggregation in the smaller venules, with occasional aggregation in the larger ones and in the capillaries.
3 = Aggregation in the arterioles, with or without intermittent plugging of the tip of the arterioles and capillaries. (Consistent heterogeneous aggregation appeared in the capillaries and venules.)

TABLE 3.—*The Relationship between the Degree of Intravascular Erythrocyte Aggregation (E.A.) and Age in Diabetic and "Healthy" Subjects*

Grading of E.A.	Group 1 Children 4–15 years				Group 2 Young Adults 16–35 years				Group 3 Middle Age 36–55 years				Group 4 Old Age 56–75 years			
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
	%				%				%				%			
Diabetic subjects	13	40	27	20	4	10	46	40	8	14	38	40	2	18	44	36
"Healthy" subjects	86	10	4	0	73	23	3	0	60	23	13	3	37	30	30	3

Table 3 illustrates the result of the grading of the intravascular erythrocyte aggregation in the nondiabetic and in the diabetic subjects. In the vast majority of "healthy" children and "healthy" young adults, there was no aggregation present in any vascular segment. On the other hand, various degrees of aggregation in the venules and capillaries were seen in 40 per cent of the middle age group and 63 per cent of the old age group. There was also a tendency for the "healthy" elderly subjects to show more severe degrees of aggregation. A χ^2 test showed that the aggregation phenomenon was significantly increased in the 2 older age groups as compared to the 2 younger ($\chi^2 = 26.85$, $p < 0.01$, $n = 2$).

The finding that red cell aggregates were not observed in the arterioles of "healthy" subjects is of particular significance. Only 2 cases, both in the elder age groups, were inconsistent with this finding. These may have had a disease process not revealed by the preliminary interview.

However, intravascular aggregation of the red cells with a marked decrease in the rate of blood flow was observed in a very high percentage in all the diabetic groups (87, 96, 92, and 98 per cent from the young to older groups, respectively). In all the diabetic groups except for the children, the severity of the aggregation was of the same degree. In the children (group 1) the aggregation phenomenon was significantly less severe than in the other age groups (groups 2, 3, and 4) ($\chi^2 = 26.46$, $p < 0.01$, $n = 2$). Thus, the diabetic subjects showed little evidence of change due to aging, while the nondiabetic subjects showed a significant relationship of the degree of aggregation to age. A striking difference was present between the incidence and degree of erythrocyte aggregation in the diabetic and in the nondiabetic subjects ($\chi^2 = 185.71$, $p < 0.01$, $n = 2$). This difference is particularly brought about by the presence in the diabetic patients of aggregates that could be seen to plug intermittently the tips of the terminal arterioles (grade 3). This aggregation was associated with particularly marked slowing of the rate of blood flow in the capillaries and venules

DISCUSSION

The low range of magnification provided by the ophthalmoscope makes impossible observations of the capillaries and the small branches of arterioles and venules in the retina. Thus, the initial pathologic changes in the development of diabetic retinopathy cannot be observed. By using the stereoscopic dissecting microscope on the easily accessible bulbar conjunctiva, this disadvantage can be overcome. The changes in the conjunctival vessels may be qualitatively or quantitatively different from those lesions found in the retina and in the kidney glomeruli. However, it is possible that such differences in vascular pathology may be explained by local factors such as the specific morphology of the retinal and kidney vascular beds and the high metabolic rate of both these tissues.

The description of the alterations in the conjunctival vascular bed has been based only on clearly definable and recognizable changes. Therefore the data present an incomplete biomicroscopic picture. Despite this fact, it is felt that classification and analysis give an approximate outline of the changes that occur in this tissue in response to age and to diabetes.

By the study of "healthy" children in whom the aging changes have not influenced and distorted the vascular components, it was possible to outline the characteristics of the normal,

healthy, functioning vascular bed. The smaller blood vessels showed a regular configuration in which the ratio between the diameter of the arterioles and the accompanying larger venules was 1:3 to 1:2. The blood flow was optimal without red cell aggregation, and there was no edema present in the perivascular tissue (fig. 6).

As indicated by the study of "healthy" older nondiabetic subjects, the degenerative changes in the peripheral vascular bed apparently caused by normal aging were widespread and involved alterations in the vessel walls, in the perivascular tissue, and in the characteristics of the blood flow in the capillaries and smaller venules. All these changes became progressively severe with increasing age. However, there appeared to be an abrupt acceleration of the aging changes between the ages of 40 and 50. This fact was exemplified in the study by the significant increases in venular irregularities, sacculations, perivascular "hyaline" infiltration, and aggregation of the circulating blood in the subjects above the age of 35.

The irregularities in the configuration of the terminal arterioles were probably evidence of arteriolosclerosis because this change was persistent and was related to aging. The only definable capillary change was a characteristic angular tortuosity of the venous part. This change was not related to advancing years. However, it should not be concluded that a general distortion in the capillary network is not a part of senescence. It was apparent that the capillary network in children and young adults was orderly and regular, while in the older patients the network became progressively more irregular. Functionally, this implies that in older individuals the capillaries are not evenly distributed and hence may not provide the tissues with normal supplies of oxygen and metabolites. The frequent and marked changes in the configuration of the venules of older subjects may influence the rate of blood flow, thus causing a situation that is favorable to the settling of the red cell aggregates and may lead to formation of microthromboses.

"Hyaline"-like deposits in the conjunctival tissue are a common macroscopic and microscopic sign of senescence and occur most often in the exposed triangular part of the conjunctiva at some distance from the limbus. Fuchs[13] paid considerable attention to this senile change and found that patho-anatomically it consisted of an accumulation of amorphous "hyaline" material in the connective tissue ground substance associated with some hyaline degeneration of the collagen fibers. The "hyaline" material showed staining characteristics similar to fibrin. This change appears to be produced by 2 interrelated factors; senile alterations in the tissue and prolonged exposure to external and internal stimuli that produce vasomotor reactions.

In recent years attention has been drawn to the intravascular erythrocyte aggregation. The importance of this phenomenon in pathologic processes has been alternately supported, questioned, and rejected by various investigators.[14-18] Some of the disagreement seems to have been based on the inadequate grading of the intravascular clumping and on the confinement of control observations to subjects of advanced age. In this study a grading system was used, the validity of which was supported by the finding of a significant relationship between the in vitro aggregation as measured by the sedimentation rate and the degree of in vivo aggregation in the same subjects.[19] The progression with advancing age of erythrocyte aggregation in the capillaries and venules associated with slowing blood flow may explain the discrepancy in various opinions. Recently, Gillems and Morgan[20] have shown that sedimentation rate increases with age. The aggregation phenomenon appears to be related to increases in relative or absolute concentrations of the globulin and fibrinogen fractions in the blood.[19, 21, 22] The normal protein pattern becomes progressively altered with aging, and possibly it is the cause of the intravascular erythrocyte aggregation in older subjects.[23] Of particular importance is the present finding that intravascular erythrocyte aggregation was not observed in the *arterioles* of healthy subjects. This supports the original statement by Bloch[22] following his observations on more than 3000 healthy and diseased individuals: "To date no person has been seen in whom there is a significant and continuous retardation of blood

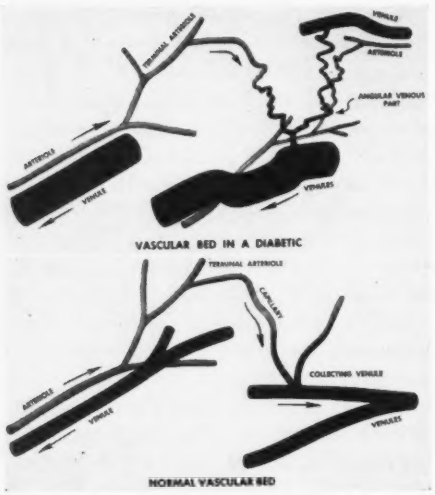

FIG. 6. The vascular bed of a young diabetic subject as compared to a normal vascular bed.

flow by erythrocyte aggregates through the *arterioles* who is not ill."

Diabetes appears to affect the small blood vessels in 2 different ways: (1) by producing lesions that are indistinguishable from those of normal aging and (2) by producing capillary and venular changes that are characteristic of diabetes and unrelated to the aging process. Both kinds of alterations are present in diabetic subjects of all ages, but their incidence is influenced strongly by the age of onset of diabetes and the chronologic age of the subject. Thus, the vascular lesions occurring in the older patients consist predominantly of the changes indistinguishable from those of aging, while in the younger patients the lesions consist mostly of the characteristic diabetic capillary and venular alterations.

The aging changes in the diabetic subjects are the same as those in the "healthy" subjects, i.e., arteriolar and venular irregularities, "hyaline" infiltration of the perivascular tissue, and intravascular aggregation of red cells with slowing of blood flow. However, all these changes appear earlier in the diabetic than in the nondiabetic subjects, and in all diabetic groups the incidence is significantly increased. Thus, the aging process appears to be accelerated. This is particularly evident in the comparison of young diabetic subjects with their controls and becomes less striking in the older age groups.

The characteristic changes of diabetes are observed particularly in the young individuals. The vascular alterations consisted of tortuous elongations of the venous part of the capillaries and of the venules, as well as changes in the arteriolar-venular ratio associated with the presence of edema in the perivascular tissue (fig. 6). In order to elucidate further the nature of these characteristic changes, serial observations were made in a large number of young diabetic subjects for a period of 10 months.[24] In this study it was demonstrated that the changes in the caliber of the arterioles and venules (A/V ratio) associated with exudation through the venular walls were a reversible pathologic vasomotor response. The elongation of the venous part of the capillaries and venules was apparently an irreversible change and most likely caused by a proliferation of the endothelial cells associated with degeneration. It thus appears that proliferation and pathologic vasomotor responses that particularly involve the venules take place to a greater extent in the young diabetic than in the older diabetic subjects. It should be noted that the retinal pathology appears to parallel this finding. During recent years it has become evident that the retinopathy of young long-term diabetic subjects differs somewhat from that of middle-aged and elderly diabetic subjects. While the retinopathy in the elderly diabetic patients tends more to show exudative benign changes, the retinopathy in the young patients is characterized by marked degenerative changes in the veins, formation of capillary microaneurysms and proliferation of vessels.[2, 25] Lundbaek[3] also demonstrated that the venous lesions were statistically related to the young long-term diabetic subjects as compared to the older long-term diabetic ones.

Capillary microaneurysms of the type present in the retina of diabetics were not observed in the bulbar conjunctiva. According to Ashton[26] such lesions are apparently not present in tissues other than the retina and possibly the glomeruli of the kidneys. This suggests that the formation of microaneurysms is associated with local factors in the retinal tissue such as special capillary morphology,

arrangement, functional need, or high pressure. The elongation of the venous part of the capillaries, which was found to be an early change in the conjunctiva, has likewise been demonstrated as an early finding in the retina, and studies suggest that the proliferation of new vessels start from such elongated and looped capillaries.[27] Thus, some of the capillary changes in the conjunctiva appear similar to those of the retina. The correlation between the degree of conjunctival changes in the diabetic children and the duration of the disease,[12] as is also true for diabetic retinopathy, supports the concept that the changes in the smaller blood vessels of the conjunctiva and of the retina are related. The pathologic vasomotor responses in the smaller conjunctival vessels are present very early in the diabetic condition, many years before retinopathy can be observed with an ophthalmoscope.[28] Observations suggest that the reversible responses are fundamental to the mechanism leading to the formation of the diabetic microangiopathy.[29]

The most obvious difference between the diabetic and the "healthy" subjects was the rate of blood flow through the capillaries and the venules. In the diabetic subjects discontinuous and slow blood flow was brought about by the venular distention and a severe degree of intravascular erythrocyte aggregation, plugging the tips of the arterioles. The intravascular erythrocyte aggregation seems to be related to changes in proteins in the plasma of diabetic patients. There is evidence[18, 19, 22, 30, 31] to indicate that certain globulins, when in excess in the plasma, form a surface film on intravascular phase boundaries by which aggregates of erythrocytes are formed. Changes in the physical characteristics (viscosity, tensile strength) of this surface film may affect the sizes of the erythrocyte aggregates and furthermore interfere with the passage of oxygen and metabolites through the capillary and venular walls. Changes in the serum proteins and their conjugates have been found not only in diabetic subjects with well-established vascular disease but also in diabetic subjects without clinical evidence of "complications." These changes are characterized by an increase in α_2-globulin and in β-lipoprotein and a decrease in albumin.[2, 32-34]

The stasis associated with distention of the venules leads to intermittent seepage of plasma through the venular walls out into the perivascular tissue. Depending upon the degree and duration of exudation and the rate of resorption, proteins may be deposited. This may explain, in part, the early and extensive appearance of "hyaline" infiltration in the conjunctival tissue of young diabetic subjects.

This study strongly supports the supposition that the vascular lesions in the retina and glomeruli of the kidney are manifestations of one slowly developing, generalized disease in the smaller blood vessels. Even though the normal age changes appear to be accelerated in diabetes, the characteristic capillary and venular alterations in the vascular bed of the diabetic subjects emphasize that the vascular changes occurring in this disease are different from those of normal aging and "arteriosclerosis."

Summary

A comparative biomicroscopic study has been made of the bulbar conjunctival vascular bed of 220 diabetic and 175 "healthy" subjects of various ages. Vascular, perivascular, and intravascular alterations taking place in diabetic and nondiabetic subjects along with aging have been classified and analyzed.

The study of healthy children, in whom aging changes have not influenced and distorted vascular components, helped define the characteristics of a normal, healthy, functioning vascular bed. The smaller blood vessels showed a regular configuration with a ratio between the arterioles and the accompanying larger venules of 1:3 to 1:2. The blood flow was optimal without red cell aggregation and there was no edema in the perivascular tissue. The significant vascular changes along with aging occurred as irregularities in the terminal arterioles and in the larger and smaller venules. "Hyaline" infiltration in the perivascular tissue was correlated to age as was intravascular erythrocyte aggregation associated with slowing of blood flow in the capillaries and venules. Thus, all the degenerative changes in the peripheral vascular bed became progressively more severe with increasing age.

The significant vascular changes in the dia-

betic subjects consisted of (1) lesions that were indistinguishable from those of normal aging and (2) capillary and venular alterations, exudation, and arteriolar plugging of erythrocyte aggregates that were characteristic of diabetes and were unrelated to the normal aging process.

Both kinds of changes were present in diabetic subjects of all ages, but their distribution was influenced strongly by the age at onset of diabetes. Thus the vascular lesions occurring in the older patients consisted predominantly of changes indistinguishable from those of aging, while in the young patients the lesions consisted mostly of the characteristic diabetic alterations.

The diabetic capillary venular characteristics were of 2 types, i.e., reversible and irreversible changes. The reversible changes were seen as various degrees of venular distention and arteriolar narrowing and formed a set of pathologic vasomotor responses. The irreversible lesions consisted of elongations of the venous part of the capillaries and venules accompanied by evidence of degeneration.

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Summario in Interlingua

Un comparative studio biomicroscopic esseva executate in le vasculatura del conjunctiva bulbar de 220 diabeticos e 175 subjectos normal de varie etates. Le alterationes vascular, perivascular, e intravascular que occurre in diabeticos e non-diabeticos in le curso del progresso de etate esseva classificate e analysate.

Le studio de juveniles normal, in qui alterationes debite al etate ha non ancora influentiate e distorquite le componentes vascular, esseva de adjuta in definir le characteristicas de un normal vasculatura. Le minor vasos sanguinee monstrava un configuration regular con un proportion de 1 a 3 o 1 a 2 inter arteriolas e le plus grande venulas accompaniante. Le fluxo de sanguine esseva optimal sin aggregationes erythrocytic, e il habeva nulle edema in le histos perivascular. Le significative alterationes vascular que occurreva in le curso del progresso de etate se manifestava como irregularitates in le arteriolas terminal e le venulas major e minor. Infiltrationes hyalin in le histos perivascular esseva correlationate con le etate. Le mesmo vale pro le aggregation erythrocytic intra vascular associate con relentamento del fluxo sanguinee in capillares e venulas. Assi omne le alterationes degenerative in le vasculatura peripheric deveniva progressivemente pejor in le curso del progresso de etate.

Le alterationes vascular que esseva significative in le individuos diabetic consisteva de (1) lesiones non distinguibile ab lesiones occurrente in individuos normal in le curso del progresso de lor etate e (2) alterations capillar e venular, exsudation, e obstruction arteriolar per aggregatos erythrocytic que esseva characteristic de diabeticos e que non esseva connectite con le normal processo del avantiamento del etate.

Ambe typos de alterationes esseva presente in diabeticos de omne etates, sed le distribution de iste alterationes esseva fortemente influentiate per le etate del patiente al tempore del declaration de su morbo. Assi le lesiones vascular in patientes de etate plus avantiate consisteva predominantemente de alterationes que non esseva distinguibile ab illos debite al progresso de etate, durante que le lesiones in le patientes plus juvene consisteva predominantemente de alterationes characteristicamente diabetic.

Le characteristicas capillar e venular in diabeticos esseva de 2 typos, i.e. illos esseva (1) alterationes reversibile o (2) alterationes irreversibile. Le alterationes reversibile se manifestava como varie grados de distension venular e de restriction arteriolar e formava un serie de pathologic responsas vasomotor. Le alterationes irreversibile consisteva de elongationes del parte venose del capillares e del venulas es esseva accompaniante per signos evidente de degeneration.

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Studies of the Mitral Valve

II. Certain Anatomic Features of the Mitral Valve and Associated Structures in Mitral Stenosis

By Ian E. Rusted, M.D., Charles H. Scheifley, M.D., and Jesse E. Edwards, M.D.

Knowledge of the structural changes in the commissures, cusps, and chordae tendineae is important to the understanding of the pathologic physiology of mitral stenosis and its surgical correction. Study of 70 hearts with mitral stenosis disclosed that a frequent cause of the obstruction was commissural fusion or shortening of the chordae tendineae or both. In a small percentage of hearts, mitral stenosis appeared to result principally from rigidity of the valvular leaflets. Measurements of the various components of the mitral valve in normal hearts have been given in a previous paper. In this communication, comparable measurements for these structures in 50 hearts with mitral stenosis are presented.

A STUDY was made to compare details of structure that have been described in normal mitral valves[1] with corresponding details in valves affected by rheumatic mitral stenosis. An attempt has been made to improve understanding of the fundamental changes involved in this condition. An anatomic classification of rheumatic mitral stenosis into 4 types has been developed from these considerations.

Methods and Material

Seventy hearts preserved in formalin in the pathologic collection of the Mayo Clinic formed the basis for this study. Severe mitral stenosis was present in the majority of these specimens, but a few examples of milder forms of stenosis were retained. Mitral stenosis was the essential lesion in each heart, although some showed mild degrees of rheumatic involvement of other valves, particularly the aortic valve. Each of the hearts used in this study was well preserved.

The 70 hearts represented 44 female patients and 26 male patients. The females ranged in age from 13 to 84 years, and the males ranged from 19 to 73 years. The average age of the females was 46 years, and that of the males was 45.

One phase of the study was to determine whether or not the same anatomic basis for mitral stenosis was present in each of the 70 hearts. A second phase of the investigation involved measurement of the various components of the mitral valve. This was done in 50 of the 70 hearts and the results were compared with the findings in a series of normal hearts previously reported by us.[1] Of the 50 hearts thus measured, 18 represented male patients and 32 represented female patients. The average age at death was 44 years (range of 19 to 66 years) in the former group and 43 years (range of 13 to 83 years) in the latter. The ages of these 50 patients were similar to those of the patients who had the normal hearts that we had studied previously and from which data were used as a basis for comparison. The cause of death in 33 of the 50 cases was attributable to the mitral stenosis, congestive cardiac failure being the chief manifestation among these patients. The remaining 17 patients died of causes not directly related to the mitral stenosis. Since the average measurements of the various components of the mitral valve in the study of normal hearts differed only slightly in men as compared with women, all 50 hearts with mitral stenosis were placed in 1 group for the purpose of obtaining average measurements. The terms applied to the components of the mitral valve and the methods for measuring these are the same as those employed in our earlier report,[1] except that the measurements of cusps and commissures include thickened portions as well as the relatively normal pliable parts.

Observations also were made on the frequency of calcification in the mitral valve and the situations in which it was found.

From the Mayo Foundation and the Mayo Clinic, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota, Rochester, Minn.

Classification of Mitral Stenosis

Examination of the 70 hearts with mitral stenosis made it apparent that there was no uniformity in the changes among the various components of the mitral valve. For example, the stenosis in some hearts depended on the changes in the chordae, in others on the changes in the valvular leaflets or in the commissures, and in still others on combinations of changes

TABLE 1.—*Types of Mitral Stenosis in Seventy Hearts*

Type of stenosis	Cases
Commissural	22
Cuspal	11
Chordal	6
Combined	
Cusp and commissure	10
Chordae and commissure	10
Chordae, cusp, and commissure	11
Total	70

in these 3 structures. Four types of mitral stenosis were noted, namely, (1) commissural, (2) cuspal, (3) chordal, and (4) combined. The frequency of occurrence of these 4 types is presented in table 1.

Commissural Type. As the name implies, this type has the severest changes in the commissures (fig. 1*a* and *b*). The changes in the leaflets and chordae tendineae are relatively minor and do not appear to contribute materially to the stenosis. Commissural stenosis was present in 22 of the 70 cases.

Two subdivisions of the commissural type may be delineated. In the first, the commissure retains its normal depth but is abnormal by virtue of increase in thickness and loss of pliability. Such a commissure is often thickened with calcified material. Since the depth of the commissure is not increased, the greatest diameter of the valvular orifice is not affected by the change. In the second subgroup, the depth of the commissure is increased because of fusion of the valvular leaflets in the vicinity of the commissure. The newly formed component of the commissure is continuous with the original commissure. Because the depth of the commissures is increased, it follows that the greatest diameter of the valvular orifice is reduced. The original commissure in this second subgroup may or may not be thickened and stiff. In each of these 2 subgroups, the 2 commissures (anterolateral and posteromedial) may be affected equally or 1 may be predominantly involved, so that the changes in this 1 commissure may even constitute the only cause of the stenosis.

Cuspal Type. The essential abnormality in this type is conversion of the mitral leaflets, or cusps, into stiff, rigid, and often leathery membranes (fig. 1*c* and *d*). The anterior leaflet usually is involved to a greater extent than is the posterior one. In each leaflet, the greatest amount of fibrous thickening extends inward for 1 cm. or more from the free edge of the leaflet. The thickness generally is most pronounced at the line of closure. The commissures and chordae may be affected to minor degrees but these play an insignificant role, if any, in mitral stenosis of the cuspal type. The rigidity of the cusps themselves apparently is the essential cause of the abnormal function in this change.

Chordal Type. In this type, the chordae are grossly involved and are thickened, shortened and frequently fused (fig. 1*e*). The shortening as well as the fusion appears to contribute to the stenosis. It will be recalled that each mitral leaflet makes attachment with both the anterolateral and posteromedial sets of chordae. This anatomic phenomenon, in which each leaflet is connected to a pair of opposing chordae, probably plays a role in reducing the flexibility of the leaflets when the chordae are shortened. As each set of chordae to 1 leaflet is shortened, tension is placed on the leaflet so that its mobility is reduced, even though its own structure may be unaffected.

Fusion of the chordae, which usually is associated with severe degrees of chordal shortening, produces a new membrane continuous with commissural tissue. If chordal shortening is pronounced, the valvular leaflets tend to be pulled downward. In this event, the distorted leaflets, coupled with the chordal fusion, convert the valve into a funnel-shaped structure. In the chordal type of change leading to mitral stenosis, abnormalities in the leaflets and commissures are of relatively minor significance.

Combined Type. Combinations of 2 or 3 of the foregoing changes may lead to mitral stenosis (figs. 2 and 3). One combination is that in which the commissures are thickened but not increased in depth and at the same time the free portions of the leaflets are thickened. In this type, the chordae are thickened only mildly, if at all, and appear not to be significantly shortened. In other instances, fusion of the valvular leaflets, causing elongation of the

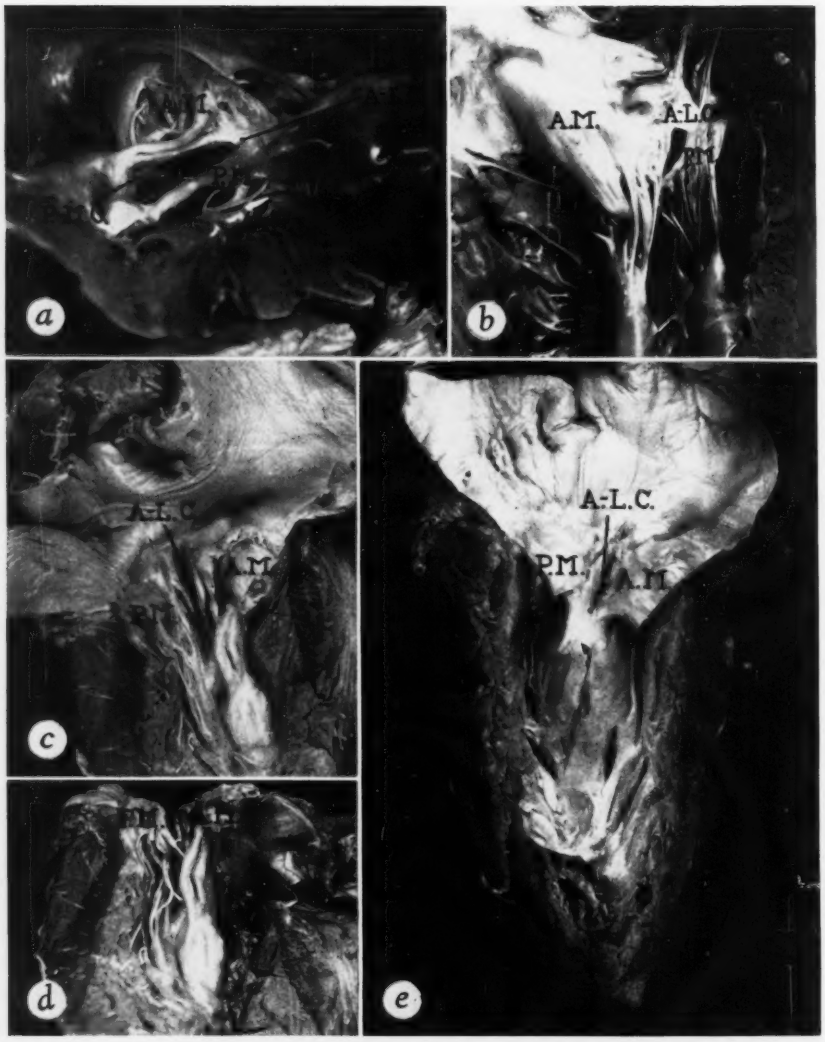

FIG. 1. Anatomic types of mitral stenosis. *a*. Commissural type of stenotic valve viewed from below. Some thickening of the chordae also is present. *A.M.* = anterior mitral leaflet; *P.M.* = posterior mitral leaflet; *A.L.C.* = anterolateral commissure; *P.M.C.* = posteromedial commissure. These abbreviations also apply to the remaining figures. *b*. Commissural type viewed from below. The leaflets are joined at the commissures, the anterolateral commissure being shown better than the posteromedial one. The chordae are essentially normal. *c* and *d*. Cuspal type of mitral stenosis illustrated in the region of the anterolateral commissure. Thickened leaflets are shown in *c*, in which the chordae are thickened and fused but not shortened. The stenosis was considered to be mainly on the basis of the dense changes in the valvular leaflets. In *d*, the anterolateral commissure is seen from an inferior perspective, showing the fixed position of the rigid leaflets as well as the underlying chordae. *e*. Chordal type of mitral stenosis, showing the anterolateral commissure. The principal change is severe shortening and fusion of the chordae, so that the leaflets are intimately related to the underlying papillary muscle. Commissural fusion also was present in the region of the other commissure in this case.

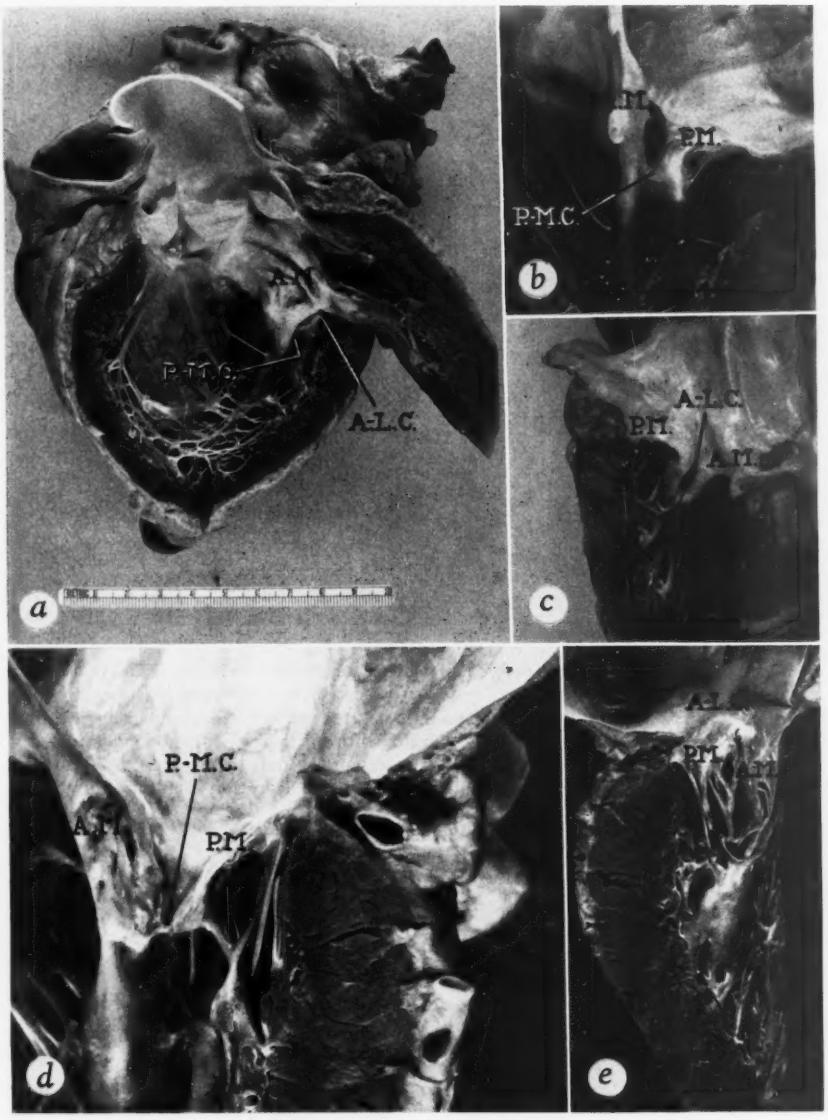

FIG. 2. Combined commissural and chordal type of mitral stenosis. *a*. The aortic valve, stenotic mitral valve and left ventricle. The intimate relationship between the anterior mitral leaflet and the papillary muscles by virtue of short fused chordae is evident. *b*. (Same case). The posteromedial commissure showing fusion of the 2 leaflets and extreme shortening with fusion of the chordae. A thrombus caps the commissure. *c*. (Same case). The anterolateral commissure, with essentially the same changes as in the posteromedial commissure. *d*. Mitral stenosis with commissural and chordal changes present in the posteromedial commissure. *e*. (Same case). Essentially normal features are present at the anterolateral commissure.

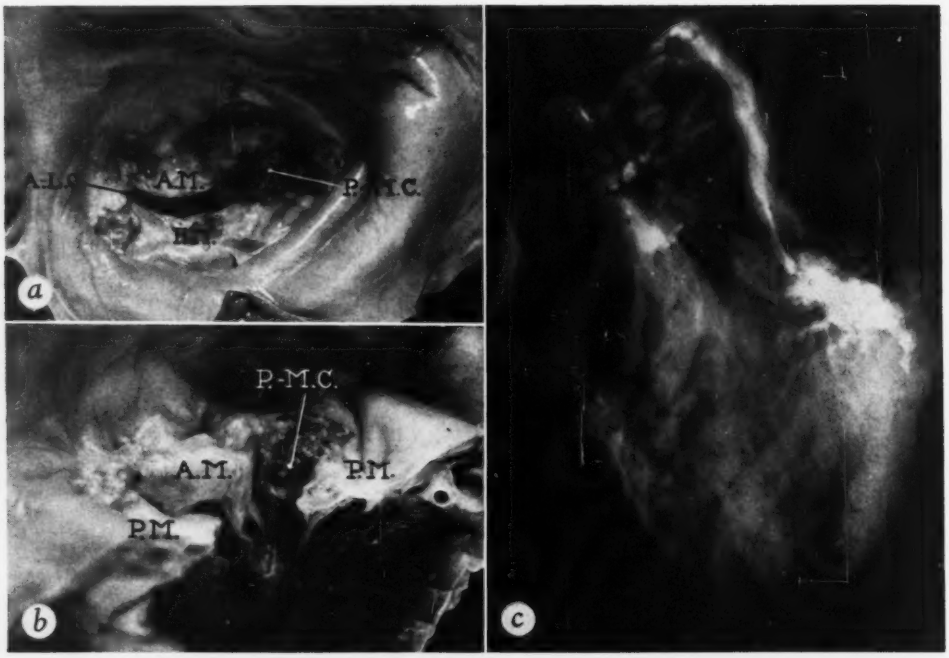

FIG. 3. Combined commissural and cuspal type of mitral stenosis. *a*. The mitral valve from above. The nobby effect resulting from calcification in the valvular tissue is evident. A thrombus is present at the posteromedial commissure. *b*. The mitral valve has been opened by a section through the posterior leaflet, and the posteromedial commissure is better exposed. The underlying chordae are only mildly involved. The stenosis is caused by fusion with calcification at the commissures and the valvular rigidity inherent in the calcification of the leaflets. *c*. Roentgenogram of the heart viewed from in front. The dense mass is indicative of the considerable degree of calcification involving the mitral valvular tissue.

commissure, frequently is associated with thickening, shortening, and fusion of the chordae.

MEASUREMENTS

As already indicated, a number of measurements were made on 50 of the 70 hearts included in the present study. These measurements are summarized in tables 2, 3, and 4.

Anterior Leaflet. The total depth of the anterior leaflet, or cusp, of the mitral valve, including pliable as well as thickened portions, averaged 2.6 cm., the range being 2.0 to 3.5 cm. The average depth of this leaflet in normal men and women has been found to be 2.2 cm., with a range from 1.6 to 2.9 cm. It is evident that the total depth of the anterior leaflet in hearts with mitral stenosis may differ little from that in normal hearts.

As has been indicated by others and from the observations on this series of hearts, it is apparent that the free portion of the leaflet may be greatly thickened while the basal portion may be relatively thin and pliable. Therefore, it was of interest to measure the depth of the thickened portion and the depth of the thinner pliable tissue in the anterior mitral leaflet of hearts with mitral stenosis. The average depth of the thickened portion that extended inward from the free edge was 1.1 cm., with a range of 0.4 to 2.0 cm. The depth of the pliable zone, which was that portion of the valve attached to the annulus fibrosus, averaged more than that of the thicker portion. The pliable zone averaged 1.5 cm. in depth, with a range of 0.6 to 2.7 cm. The thickness of the thickest portion of the anterior leaflet in these 50 hearts averaged 0.31 cm., with a range of 0.1 to 0.7 cm.

TABLE 2.—*Measurements of Components of Mitral Valves in Mitral Stenosis: Fifty Hearts*

Structure	Depth, cm.		Thickness, cm.	
	Range	Average	Range	Average
Anterior cusp				
Thick portion	0.4–2.0	1.1	0.1–0.7	0.31
Pliable portion	0.6–2.7	1.5		
Total depth	2.0–3.5	2.6		
Posterior cusp				
Thick portion	0.0–1.4	0.8	0.1–0.65	0.27
Pliable portion	0.0–1.2	0.6		
Total depth	0.6–2.2	1.3		
Anterolateral commissure				
Thick portion	0.0–1.9	0.9	0.1–0.85	0.32
Pliable portion	0.0–1.1	0.5		
Total depth	0.5–2.5	1.3		
Posteromedial commissure				
Thick portion	0.2–1.8	0.9	0.1–0.85	0.32
Pliable portion	0.0–1.9	0.3		
Total depth	0.3–2.9	1.2		

Posterior Leaflet. The total depth of the posterior leaflet, or cusp, averaged 1.3 cm., the range being 0.6 to 2.2 cm. This coincides with the measurements in normal hearts. The other measurements for the posterior cusp are summarized in table 2.

Commissures. At the anterolateral and the posteromedial commissures, the total depth from the free edge to the ring of the valve averaged 1.3 and 1.2 cm., respectively (table 2). This represents a considerable increase over the average depth of tissue at the commissural zones in our series of normal hearts, which was 0.7 cm. in women and 0.8 cm. in men, with 1.3 cm. as the upper limit of normal. In most instances of increased commissural depth, it was obvious that this had been caused by fusion of the free edges of the valvular leaflets adjacent to the commissural zone. Although averages in these 50 cases were more than the average normal values, the depth of the commissural tissue was within normal limits in more than a third of the cases. In many of the latter cases, however, the commissures were thickened and appeared to contribute greatly to the valvular dysfunction. This change was less pronounced in other instances, while the commissural zones were essentially normal in still others.

The depth of commissural tissue was 1.3 cm. or more at the anterolateral site in 22 of the 50 hearts and at the posteromedial site in 31 of the 50 hearts.

Both commissures were involved to approximately the same degree in one third of the cases; in another third, the anterolateral involvement was the more severe, whereas the posteromedial involvement was more pronounced in the remaining third and appeared to be contributing greatly to the valvular dysfunction.

Mitral Orifice. The size of the mitral orifice was 1 fingerbreadth or more in 30 of the 50 hearts.

The measurements summarized in table 3 show an average intercommissural diameter of 1.9 cm., which is less than the figure obtained by us in normal hearts, namely 2.1 cm. in women and 2.5 cm. in men. The same is true for the average anteroposterior diameter of 0.5 cm. in mitral stenosis as compared with 1.5 cm. in normal hearts with the valvular leaflets separated, which is the position of atrial systole.

The circumference of the left atrioventricular ring ranged from 7.0 to 14.5 cm., with an average of 10.4 cm. In our normal hearts, this measurement ranged from 7.5 to 11.0 cm., with an average of 9.2 cm.

Thickness of Left Ventricle. The average thickness of the midportion of the left ventricle in these 50 hearts was the same as that of normal hearts, namely 1.4 cm. However, the range was somewhat greater in the hearts with mitral stenosis, being 1.0 to 2.3 cm. as compared with a range of 1.0 to 1.8 cm. in normal hearts. A clinical diagnosis of systemic hyper-

TABLE 3.—*Miscellaneous Measurements in Mitral Stenosis: Fifty Hearts*

Measurement	Range, cm.	Average, cm.
Intercommissural diameter of valve	0.7–2.9	1.9
Anteroposterior diameter of valve	0.1–1.5	0.5
Circumference of atrioventricular ring	7.0–14.5	10.4
Thickness left ventricle	1.0–2.3	1.4
Depth left ventricle	6.0–10.5	7.7
Thickness left atrium	0.09–0.4	0.24

tension had been made in 10 of these 50 cases of mitral stenosis. The left ventricle was hypertrophied in 5 of the 6 cases in which this hypertension had been moderate or severe. In the 4 remaining cases, the hypertension had been borderline; left ventricular hypertrophy was present in 2 of these 4 cases.

Hypertension was absent in 11 cases in which the thickness of the left ventricle was greater than 1.4 cm. Anatomic evidence of associated mitral insufficiency was present in 7 of these.

Thickness of Left Atrium. Measurements were made at 3 points, all of which were remote from the orifices of the pulmonary veins. The average of these 3 measurements was taken as the average thickness of the left atrium in each case. This value averaged 0.24 cm., with a range of 0.09 to 0.4 cm. This is greater than the figures for our normal hearts, in which the average value was 0.18 cm., with a range of 0.1 to 0.3 cm.

Chordae Tendineae. Four measurements of the length of the chordae tendineae were made in each heart (table 4). At each commissure, the chordae were measured from the commissure to the apex of each of the underlying papillary muscles. The length of the chordae from the center of the anterior leaflet of the mitral valve to each of the papillary muscles also was measured.

The average length of the chordae tendineae in these 50 hearts was only slightly more than half the length of chordae associated with normal mitral valves. The average thickness was 3 times that of normal chordae (approximately 0.05 cm. in normal hearts as compared with 0.14 cm. in the hearts with mitral stenosis). In certain instances, some of the chordae were of normal size at 1 or more of the 4 locations measured, a feature attesting to the rule that all parts of a valve are not involved equally by the rheumatic process in mitral stenosis.

TABLE 4.—*Measurements of Chordae Tendineae in Mitral Stenosis: Fifty Hearts*

Measurement	Length, cm.		Thickness, cm.	
	Range	Average	Range	Average
Anterolateral muscle to commissure	0.0–1.9	0.8	0.04–0.6	0.13
Posteromedial muscle to commissure	0.0–2.2	0.9	0.04–0.6	0.14
Anterolateral muscle to anterior cusp	0.3–2.6	1.5	0.04–0.4	0.14
Posteromedial muscle to anterior cusp	0.0–2.7	1.6	0.05–0.5	0.14

TABLE 5.—*Location of Calcification Found in 31 of 50 Hearts with Mitral Stenosis*

Location	Cases
Anterior cusp	16
Posterior cusp	11
Medial commissure	10
Lateral commissure	6
Chordae	1
Total	44*

* The total exceeds 31 because calcification occurred in more than one location in some hearts.

CALCIFICATION

The presence or absence of calcification in the mitral valve and its associated structures was noted in these 50 hearts (table 5). Gross deposits of calcium were present in 31 of the 50 hearts, the deposits sometimes being found in more than one location in a given valve. The particles of calcium were thin and superficial in 5 instances. The deposits in 8 hearts were thick, firm, and bulky in 1 or more portions of the valve. In general, calcification was commoner in the valvular leaflets than in the commissural junctions.

DISCUSSION

The results of this study have reinforced our impressions as to the value of considering mitral stenosis in terms of the changes in 3 basic groups of structures, namely the commissures, cusps, and chordae tendineae, which may be affected singly or in various combinations and to different degrees.

As already indicated, the most significant changes in 22 of the 70 hearts with mitral stenosis were restricted to one or both commissures. Consideration of the combined types

adds another 31 cases in which significant commissural involvement was present. Thus, commissural changes were important in the production of mitral stenosis in 53 (76 per cent) of the hearts. In many specimens, the changes were not always equally severe at both commissures. In 1 case, for example, the anterolateral commissure showed thickening and calcification with relatively normal cusps and chordae, while the posteromedial chordae exhibited the most severe changes of all, with no significant alterations in the adjacent commissure or cusps. In another representative case, the main lesion producing stenosis was located at the posteromedial commissure, while the anterolateral portion of the valve showed milder changes in the 2 cusps, with a normal commissure.

Harken and associates[2] have contributed to the understanding of mitral stenosis and of the variations that must be anticipated by surgeons. They divided mitral stenosis into 2 anatomic groups, namely type 1, characterized by a rigid fibrous contraction of the leaflets with essentially normal chordae, and type 2, characterized by an elastic funnel with fusion of chordae. Their illustration of a characteristic stenosis of the first type, the commoner of the 2, shows a diaphragm-like structure rather than the funnel shape so frequently attributed to a stenotic mitral valve. This diaphragm-like configuration was almost twice as common as the funnel-shaped deformity in our series of cases.

With regard to stenotic lesions resembling diaphragms, it is not always true that a continuous zone of rigid tissue is present about the orifice. We have noted previously that one commissural region may be much more severely involved than the other and that approximately equal involvement of both halves of the valve was present in only half of our cases.

While it is sometimes helpful to think in terms of a valve shaped like a diaphragm or a funnel, this is not always sufficient. For instance, both funnel and diaphragm types were encountered in all 4 of the groups of mitral stenosis that we have described. Funnel-shaped valves occurred even when the chordae were relatively normal; conversely, diaphragm-like structures often existed even though the chordae were fused and shortened.

Because the valvular leaflets were often thickest at their junction with the chordae tendineae, one might be tempted to assume that the process causing the thickening of the chordae simply had extended into the cusp, or vice versa. This may be true in some cases, but examples were observed in which the cusps of the valves were thickened at the point of junction with chordae tendineae, even though the chordae appeared to be normal. Conversely, thickening of chordae tendineae with adhesion of adjacent chordae was observed in hearts in which changes in the leaflets were minimal. It was of interest to find that the chordae tendineae in mitral stenosis averaged one half the length of normal chordae and were 3 times as thick.

It has not been recognized generally that both the anterior and posterior leaflets in hearts with mitral stenosis may be normal in depth. This observation has a bearing on the common assumption that the ring of the mitral valve is smaller than normal in mitral stenosis, an assumption that often was not true in this study. In fact, there appeared to be a definite tendency toward dilatation of the valvular ring, a tendency referred to by Coombs,[3] in 1924. One might assume that this change would cause varying degrees of mitral insufficiency, but in this connection one should recall our observation that the normally large anterior cusp may become larger than normal in some patients who have mitral stenosis.

Calcification may occur in any part of the mitral valve or its associated structures but it was found most frequently in the leaflets and in the commissural regions. The presence of calcification did not necessarily indicate that the mitral stenosis was severe, although this was true sometimes.

Summary

An anatomic study has been made of 70 hearts in which mitral stenosis was present. The changes producing mitral stenosis in these cases have been classified into 4 groups, namely, commissural, cuspal, chordal, and combined types. Diaphragm-like and funnel-

shaped structures were encountered in all 4 groups, the former being twice as common as the latter.

The stenosis in 53 hearts (76 per cent) belonged to either the commissural or the combined type. Significant changes at one or both commissures were present in all the combined types.

In one third of the cases, the posteromedial commissure was severely involved in the absence of significant changes in the anterolateral commissure.

In approximately half of the 50 specimens on which detailed measurements were made, the depth of commissural tissue was greater than 1.3 cm., the figure that is considered to be the upper limit of normal. Other measurements were recorded and compared with corresponding measurements made in normal hearts.

Calcification was observed in 31 of 50 hearts.

Summario in Interlingua

Esseva executate un studio anatomic de 70 cordes in que stenosis mitral esseva presente. Le alterationes effectuante le stenosis mitral in iste casos esseva gruppate in 4 classes secundo que illos esseva commissural, cuspidal, chordal, o combinate. Structuras de forma diaphragmatic o infundibular occurreva in omne le 4 classes, sed le formas diaphragmatic esseva duo vices plus frequente que le formas infundibular.

Le stenosis de 53 cordes (76 pro cento del serie total) pertineva al typos commissural o combinate. Alterationes significative a un o a ambes del commissuras esseva presente in omne casos del classe combinate.

In un tertio del casos le commissura posteromedial esseva severmente involvite sin que alterationes significative esseva notabile in le commissura anterolateral.

Mesurationes detaliate esseva executate in 50 del specimens, e in circa 50 pro cento de illos le profunditate del histos commissural esseva plus que 1,3 cm. Isto es le valor que es considerate como le limite superior de normalitate. Altere mesurationes esseva registrate e comparate con le valores correspondente trovate in cordes normal.

Calcification esseva observate in 31 ex 50 cordes.

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Pressor and Depressor Responses to Tilting in Hypertensive Patients

By ROBERT S. GREEN, M.D., ARNOLD IGLAUER, M.D., AND RALPH C. SCOTT, M.D.

The responses of intra-arterial blood pressure to passive head-up and head-down tilting are described for 50 patients with well established hypertension and compared to results obtained in subjects with normal cardiovascular systems. This study indicates that abnormal depressor and pressor responses are present in many patients with hypertension, that depressor reflexes are independent of pressor reflexes, that marked variations of depressor and of pressor reflex activity occur between hypertensive patients, but that the combination of depressor-pressor responses in a given patient usually remains constant.

IN 1895 Leonard Hill[1] concluded from his experimental work on the blood pressure and heart rate of animals that the effect of changing the position afforded a most delicate test of the vasomotor mechanism. The development of accurate methods of continuous recording made it possible to confirm these conclusions in man.

Previous studies[2, 3] of normal subjects established a definite pattern of blood pressure and heart rate in response to tilting. During a tilt, an immediate hydrostatic change of blood pressure always occurred at the level of the aortic arch due to the effect of gravity on the central blood column. Thus, during the tilt to the head-down position the blood pressure rose and during the tilt to head-up position the blood pressure fell. The elevated pressure produced by the head-down tilt was followed by a depressor response and the fall of pressure produced by the head-up tilt by a pressor response. In both instances the blood pressure returned to approximately the same level for an individual within 18 sec. regardless of position. Comparable results to head-down tilting have been reported by Wilkins, Bradley, and Friedland.[4]

The present report deals with similar studies in 50 patients with hypertension. The hydrostatic alterations of pressure during tilting were similar to those obtained in normal subjects. However, following tilting, striking and varied differences from the normal reflex pattern often occurred.

METHOD

Intra-arterial radial blood pressure was recorded continuously during and following tilting in 50 ambulatory patients with sustained hypertension and compared with the records obtained previously in 20 normal subjects.[2, 3]

Forty-five patients were tilted at a moderate rate (5 sec. per tilt) between the 30° head-up and the 30° head-down positions. Each position was maintained for at least 20 sec. Five patients in earlier experiments were tilted between the 20° head-up and the 45° head-down positions. The tilt to each position was repeated at least 3 times in all patients. In addition, the blood pressure was usually recorded in the horizontal position before and following tilting. Ten of these patients were restudied on one or more occasions after periods of time that varied from 1 week to 18 months.

The degree and rate of tilting remained constant by means of an electrically operated table. Braces supported the patients securely, so that they were comfortable throughout the tilt and no muscular activity was required to maintain the position. The arm was placed on a support in the plane of the table top perpendicular to the body whereby the radial artery remained at the level of the shoulder throughout the tilt. Pressures recorded with the arm in this position indicated pressure changes at the level of the aortic arch.[3]

The blood pressure was determined in the radial

From the Department of Internal Medicine, University of Cincinnati College of Medicine; the Cardiac Laboratory, Cincinnati General Hospital; and Memorial Heart Laboratory, St. Mary's Hospital, Cincinnati, Ohio.

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artery by means of a Statham strain gage adapted to record through a string galvanometer electrocardiograph.[4] A 1½-inch, 20-gage needle was used for the arterial puncture.

Results

Normal Subjects. Hydrostatic changes in blood pressure occurred during tilting (see fig. 1 and 2). With the arm maintained at the shoulder level the blood pressure always rose during movement to the head-down position (average rise 19/16 mm. Hg) and fell during the movement to the head-up position (average fall 14/13 mm. Hg).

A depressor response followed the hydrostatic elevation of head-down tilt (average fall 13/13 mm. Hg); a pressor response followed the hydrostatic fall of the head-up tilt (average rise 13/13 mm. Hg). In both positions these responses returned the blood pressure within 18 sec. to a level differing not more than 5/5

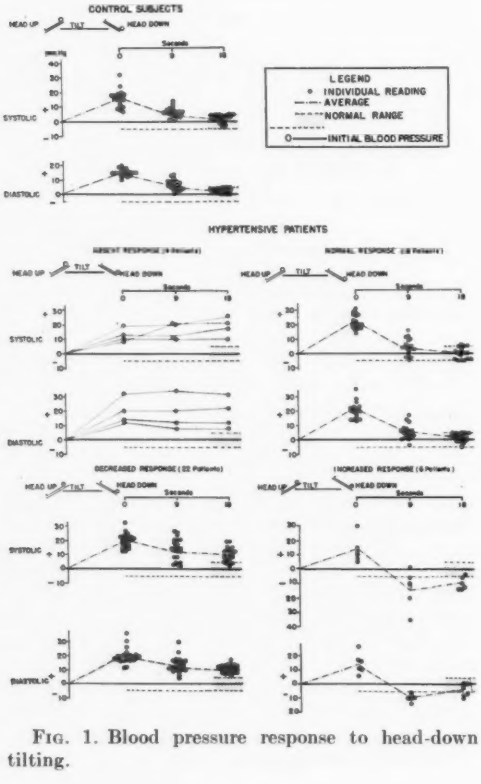

Fig. 1. Blood pressure response to head-down tilting.

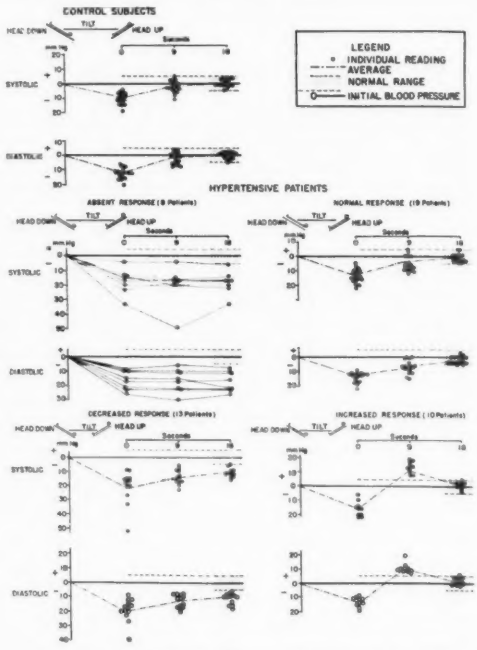

Fig. 2. Blood pressure response to head-up tilting.

mm. Hg from the initial pressure. During the depressor response the blood pressure did not fall more than 5/5 mm. Hg lower than the initial head-up pressure. During the pressor response the blood pressure did not rise more than 5/5 mm. Hg above the initial level. Each subject showed similar response on successive tilts. Five subjects studied at intervals of 1 to 3 weeks had no change in response to tilting.

Hypertensive Patients. Hydrostatic changes in blood pressure always occurred during tilting (see fig. 1 and 2). The average elevation during the head-down tilt was 19/17 mm. Hg. The average fall during the head-up tilt was 19/15 mm. Hg.

In 11 patients the depressor-pressor responses following tilting conformed to the normal pattern. Five patients were more than 70 years old; of these 3 had known hypertension for at least 10 years. The other 6 patients had sustained no apparent damage to the brain, kidneys, or heart.

There were 7 additional patients who had a normal depressor response. In 5 of these, however, the pressor response was increased and

n the other 2 the pressor response was de-reased.

In 4 patients almost no depressor or pressor esponse occurred, i.e., the blood pressure ollowing the tilt remained at the level produced y the hydrostatic effect of the tilt. One of these atients had a pheochromocytoma. A second atient died of uremia and at autopsy had rteriolar nephrosclerosis. A third patient had evere congestive heart failure complicated by enal insufficiency. In the fourth patient, hy-ertension had developed during pregnancy.

There were 22 patients in whom a decreased depressor response occurred following tilting to the head-down position, i.e., the blood pressure after 18 sec. in the head-down position was more than 5/5 mm. Hg above the blood pressure recorded in the erect position. In these patients pressor activity following the head-up tilt varied. It was classified as normal in 7, increased in 4, decreased in 8, and absent in 3. In this group were 6 patients who sustained 1 or more cerebrovascular accidents and 4 who had severe retinal hemorrhages.

An increase in depressor activity was found in 6 patients. In this group the blood pressure rapidly fell within a few seconds following the head-down tilt to a level that was more than 5/5 mm. Hg lower than in the head-up position. The reading in 1 patient was 33/11 mm. Hg lower than the erect pressure 9 sec. after the head-down tilt. Patients with this type of response invariably complained of dizziness with bending down and similar maneuvers.

Pressor response following tilting to the head-up position was absent in 8 patients and in 13 patients it was decreased, in that the pressure 18 sec. after the tilt remained more than 5/5 mm. Hg lower than the initial blood pressure. Dizziness on standing was a common complaint in the patients who had diminished or absent pressor responses following tilting to the head-up position. It was not observed in the other patients.

In 10 cases the pressor response was increased in that blood pressure shortly after the head-up tilt rose rapidly to a level of more than 5/5 mm. Hg above the initial erect pressure.

Blood pressure readings were recorded during a complete cycle of tilting at least 3 times during these tests. In addition, there were 10 patients who were tested at intervals from 1 week to 18 months. The combination of depressor-pressor responses observed in a patient remained the same both on successive tilts and over an interval of time, except in 1 patient in whom a bilateral dorso-lumbar sympathectomy, D-11 to L-2, was performed. Preoperatively, this patient had a pressure of 310/173 mm. Hg. Her depressor response was normal; the pressor response was increased. One year after the operation the blood pressure was 215/130 mm. Hg. Her depressor response remained active; the pressor response was markedly diminished.

The independence of depressor and of pressor activity is demonstrated by the lack of correlation between the type of pressor and the type of depressor response in these patients. There were 18 patients with a normal depressor response; the pressor response was normal in 11 of these, decreased in 2, and increased in 5. There were 22 patients with a decreased depressor response; the pressor response was absent in 3 of these, normal in 11, decreased in 8, and increased in 4.

Discussion

Criteria chosen to classify a response as normal or abnormal were selected after analysis of the control records of normal subjects. Whereas other points of comparison might have been used, the constancy of the response at 9 and 18 sec. in the control subjects suggested comparison with similar readings obtained in hypertensive patients.

The division of response into types as used in the presentation of data is admittedly somewhat arbitrary. There were some hypertensive patients with a response that conformed to the control pattern and some in whom the separation of normal from abnormal depended on a difference of 1 to 2 mm. Hg. In the majority of the patients, however, the differences from the control responses were striking and they remained constant on repeated studies.

Apparently the depressor and pressor responses were at least partially independent of each other, since there was often variation between the type of depressor and the type of

pressor activity in a patient, e.g., one might find decreased depressor response with either absent, decreased, normal, or increased pressor response. If a single mechanism produced these adjustments, a positive correlation between the types of response would be expected. The concept of independence of depressor and pressor response has been supported by finding that dorsolumbar sympathectomy abolished the pressor activity following tilting, whereas the depressor response remained active. We have also found that atropine diminished depressor activity in normal subjects without interfering with the pressor response.[6, 7] These changes after sympathectomy and atropine indicated that the depressor-pressor responses were mediated by a reflex rather than a humoral mechanism. In addition, the onset of adjustment in control subjects occurred within a few seconds of the start of the tilt. It is hard to visualize a humoral mechanism efficient enough to reverse itself repeatedly as abruptly as occurred in the control subjects.

Several hypotheses were suggested by the observations:

1. Normal or overactive responses were usually obtained in patients who were younger or whose hypertension had caused little obvious damage, while diminution of reflex activity was associated with later, more serious manifestations of the disease such as cerebrovascular accident and retinal hemorrhage. This suggests that changes in response were associated with a complication of hypertension that in turn contributed to the seriousness of the disease.

2. Heymans and associates[7, 8] produced hypertension in animals by interfering with he depressor mechanism. Procaine block or tection of the carotid sinus nerve in human seings resulted in temporary elevations of blood pressure.[9, 10] In our series, the depressor besponse was diminished or absent in 26 rpatients. The hypertension in some of these cases may have been related to hypofunction of the "buffer mechanism."

3. Finally, it is well established that sympathectomy in man may lower blood pressure. Ten patients had an increased pressor response; this may represent an overactive sympathetic nervous system that may have been an etiologic factor in their hypertension.

Our results confirm the well-known fact that dizziness on standing may be associated with diminished pressor activity. In addition, an increased depressor response may explain the paradox of dizziness while in a bent-over position.

The pattern of depressor-pressor activity was not related to the level of the blood pressure. For instance, normal responses occurred in 1 patient who had a horizontal blood pressure of 317/175 mm. Hg, whereas the reflex responses were absent in another patient whose horizontal pressure was 180/120 mm. Hg.

Summary

Responses of blood pressure to tilting have been studied in 50 hypertensive patients and compared with findings in 20 normal subjects.

A normal depressor and pressor response occurred together in 11 patients. Variations from the normal pattern were noted in 39 patients in whom either or both responses were increased, decreased, or absent. Absent or diminished depressor activity was present in 26 patients.

Independence of depressor and pressor response has been demonstrated. Evidence has been presented that depressor and pressor responses are mediated by a neural mechanism.

The data suggest that disorder of reflex depressor as well as of pressor mechanism may be important in the etiology of hypertension.

Summario in Interlingua

Responsas al position in plano inclinate esseva studiate in le pression sanguinee de 50 patientes hypertensive. Le datos esseva comparate con constatationes correspondente in 20 subjectos normal.

Le combination de normal responsas pressorial e depressorial occureva in 11 patientes. Deviationes ab le norma esseva notate in 39 patientes. In illes le un o le altere responsa o ambe responsas esseva augmentate, reducite, o absente. In 26 patientes le activitate depressorial esseva reducite o absente.

Esseva demonstrate le independentia del responsas depressorial e pressorial. Es presentate observationes in supporto del conception

que le responsas depressorial e pressorial es mediate per un mechanismo neural.

Le datos presentate pare indicar que disordines del mechanismo del reflexos depressorial e pressorial pote esser importante pro le etiologia de hypertension.

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Perera, G. A.: Edema and Congestive Failure Related to Administration of *Rauwolfia serpentina.* J. A. M. A. **159:** 439 (Oct. 1), 1955.

In 5 patients with hypertensive vascular disease, fluid retention occurred after the administration of crude or pure alkaloids of *Rauwolfia serpentina.* None of these patients had been in failure prior to the administration of rauwolfia and all cleared when treatment ceased. One of the patients who had developed marked edema while receiving reserpine was again given the drug for a week's time. Definite pitting edema of the ankles was again apparent. It vanished once more when administration of reserpine was discontinued. In 2 patients fluid retention was severe enough to cause congestive failure. The occurrence of sodium retention during therapy with rauwolfia derivatives should be kept in mind whenever edema or congestive failure develops in patients who are taking such medications.

KITCHELL

CLINICAL CONFERENCE

EDITOR: EDGAR V. ALLEN, M.D.

Associate Editor: RAYMOND D. PRUITT, M.D.

Adult Fibroelastosis with Congenital Tricuspid Stenosis

Edited by HANS POPPER, M.D., DANIEL S. KUSHNER, M.D., AND BENJAMIN GASUL, M.D.

THIS conference was presented at Cook County Hospital, Chicago, Illinois, on February 20, 1955, as one of the regular weekly clinical-pathologic exercises of the Hospital. The conferences are modeled after the Cabot prototype, the case being presented by the clinicians as an unknown for discussion. In order to preserve the spirit and spontaneity of the original conference, editing has been limited largely to making the material more suitable for publication, selection of pertinent photomicrographs for reproduction, and documentation of pathologic interpretations by appropriate references.

CLINICAL DATA AND DISCUSSION

DR. BENJAMIN GASUL: A 39-year-old American-born married white male clerk was admitted to Cook County Hospital in November 1954 with complaints of blueness, severe shortness of breath, marked weakness, abdominal distention, and incoherence for 1 day. He had been well until 1951, when he had the first episode leading to 4 admissions to another hospital, summarized as follows:

October 1951. The patient's right foot suddenly became cold, blue, and pulseless. An embolectomy was performed but gangrene ensued and a supracondylar femoral amputation was done. Perhaps we should stop to analyze this very serious mode of onset of illness. This man, perfectly well for 36 years, suddenly developed a cold, blue, pulseless foot. This could mean arteriosclerosis with a local thrombus, a thromboangiitis obliterans, or a diabetic arteriosclerosis with gangrene; but we have no evidence for these. Deep venous phlebitis will not explain this cold, blue, pulseless foot.

What about the heart? We are given no information pertaining to the cardiac examination. What cardiac condition must be considered? The most common cause for embolization is a left-sided lesion such as rheumatic mitral valvular heart disease, which may be silent for 36 years. There could be a mural thrombus; there is no evidence of a coronary thrombosis nor of aortic valvular involvement. Therefore, the first thing to think of is a left-sided cardiac lesion, primarily mitral. Barring that, we have to consider a congenital noncyanotic type of cardiac malformation, the most common of which would be an atrial or ventricular septal defect. Even Ebstein's malformation of the tricuspid valve is a possibility. Since 20 to 30 per cent have a patent foramen ovale, it could be associated with a paradoxical embolus. Amyloidosis and some form of fibroelastosis are also possibilities.

December 1951. The patient was readmitted with a femoral artery embolus, and a left lumbar sympathectomy was performed. He then did well with a prosthesis until *August 1952*, when he was readmitted for abdominal swelling of 3 months' duration, ankle edema, orthopnea, and dyspnea, with improvement following treatment for congestive heart failure. And still nothing is said about the cardiac findings.

April 1953. The patient was readmitted with complaints of increasing edema, abdominal distention, severe dyspnea, orthopnea, nocturnal cough, and episodes of chills and sweats. Now, he had definite right and left heart failure.

From the Departments of Pathology, Medicine, and Pediatrics of the Cook County Hospital and Northwestern University Medical School, Chicago, Ill.

The chills and sweats are interesting but did they last a week or 2 or 3? If they lasted that long, the cause could be bacterial endocarditis or pericarditis. Was he treated? Did he get better because he had penicillin? Nothing is mentioned about this. Findings at that time included pulmonary rales and cardiac apex beat in the fifth intercostal space, 11 cm. from the sternum. If this is measured from the right sternal margin, it is normal; if from the midsternum, it is a little enlarged; and if from the left sternal border, it is definitely enlarged. A grade 3 systolic or grade 3 presystolic and a middiastolic murmur were heard at the apex. If he had a presystolic murmur at the apex or a middiastolic and grade 3 systolic, the chances are good that he had either mitral stenosis, with regurgitation on the basis of involvement of the mitral valve, or relative stenosis on the basis of enlargement of the left ventricle, or even a tricuspid lesion on the basis of right ventricular involvement.

Venous pressure at that time was 33 cm. of saline; circulation time was 19 sec. with ether and 30 sec. with Decholin, so both right and left sides of the heart were involved. Pericardiocentesis produced 150 ml. of brown turbid fluid, and abdominal paracentesis produced 3200 and 3500 ml. of ascitic fluid.

Roentgenograms of the chest showed slight increase of the transverse diameter of the heart, without characteristic configuration, and exaggeration of bronchovascular markings. Fluoroscopy showed "mitral stenosis with aortic enlargement; no calcification in the wall of the heart."

Dr. William Meszaros: A postero-anterior view of the chest was taken in 1951, at the time of his first illness. The heart is normal in size and shape. The lungs are clear. The chest is negative at this time (fig. 1*A*).

The second radiographic examination was performed in April 1953. The transverse cardiac diameter now appears to be increased. Measurements are not strictly comparable because the diaphragm is 1 interspace higher. However, the gross appearance indicates an increase in size of the cardiac shadow. There is some straightening of the upper left cardiac border. The lung fields remain clear.

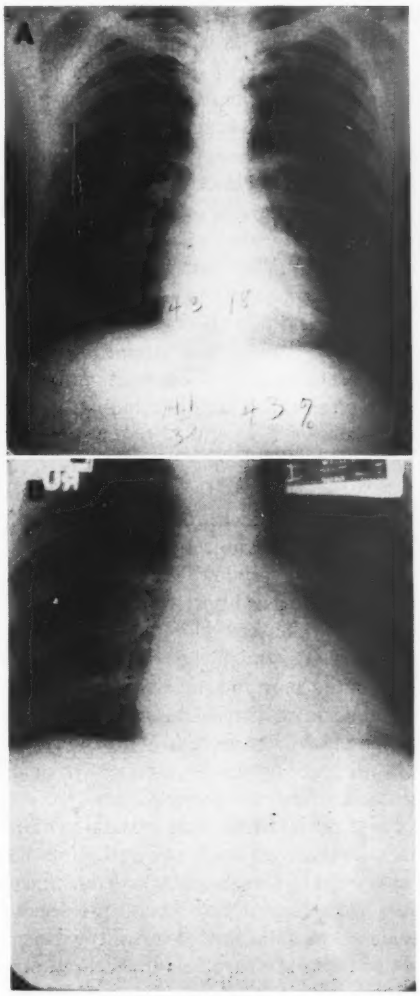

Fig. 1. *A*. Roentgenogram of chest, October 1951. *B*. Roentgenogram of chest, May 1953.

The third radiographic examination was performed in May 1953, 4 days before surgery (fig. 1*B*). A film taken with increased penetration fails to show calcification of the pericardium or heart valves. An interesting finding is the straight left heart border, which may be seen in constrictive pericarditis.

The last chest film was taken 10 days after surgery, in 1953. There is a large left pleural effusion. The heart is displaced to the right. There are no other significant findings.

DR. GASUL: The electrocardiogram on May 15, 1953, (fig. 2) shows slight depression of S-T in lead I, marked depression in lead II, diphasic T, and normal QRS. There is no evidence of right bundle-branch block as one would expect in an atrial septal defect. From the standard leads the electrocardiogram is consistent with myocardial anoxia or pericarditis. V_1 and V_2 reveal no evidence of right ventricular hypertrophy. There is marked depression of the S-T segment. The inversion of the T waves is consistent with myocardial anoxia or pericarditis. There are inverted T waves in aV_R and an elevated S-T segment, which may be a sign of anoxia. The other findings here are still consistent with pericarditis or with myocardial anoxia.

In November 1954, the tracing shows low amplitude QRS, which goes with pericarditis or shock from any cause. Again there is anoxia. The T waves are very low. There is no evidence of right ventricular hypertrophy. AV_L shows a Q and S, which could occur in a vertically placed heart. This might be a sign of clockwise rotation of the heart, which could follow pulmonary embolism with marked anoxia. But that is not too much help. Certainly no one is justified in diagnosing mitral stenosis from the electrocardiogram. Nor would I want to commit myself on interpretation of the x-ray films, which are consistent with pericarditis or with almost anything else but not with an uncomplicated atrial septal defect, because there is no evidence of definite increase in pulmonary blood flow. I will be surprised if this is an atrial septal defect or an intraventricular septal defect. The electrocardiograms are definitely against either of these conditions and merely indicate a pericarditis with anoxia. There is no evidence of coronary thrombosis.

The cardiac catheterization was very interesting because it revealed the following: normal pulmonary arterial pressure; right atrial pressure of 17 mm. Hg (20 cm. of water) with an "M"-shaped curve. Right ventricular pressure tracing showed diastolic dip and plateau. Cardiac index was 1.22 L./M.^{2}/min. at rest. What does this mean? If the pulmonary artery pressure was normal, we can assume the right ventricular pressure was normal too, because

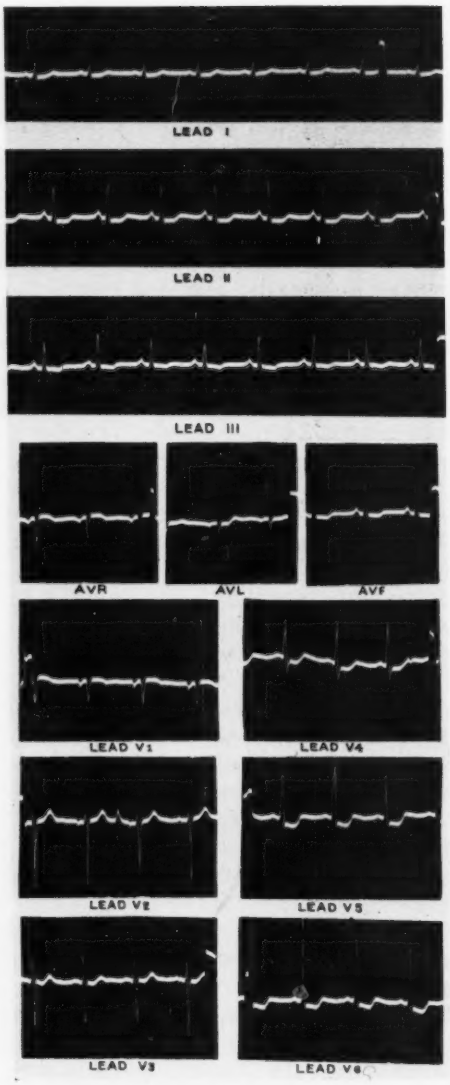

FIG. 2. Electrocardiogram, May 15, 1953.

there is no evidence of pulmonary stenosis here. If pulmonary pressure was normal and so was the right ventricular pressure, that would definitely speak against a diagnosis of mitral stenosis, even with right heart failure, because even in the presence of tricuspid regurgitation there should be some elevation of right ventricular pressure. If this were a rheumatic mitral

stenosis, I would assume there was also a tricuspid stenosis and not regurgitation. But here again, the diagnostic sign of tricuspid stenosis is a high diastolic pressure in the right atrium, even higher than in the right ventricle. We have no information on that. A right atrial pressure of 17 mm. Hg with "M" curve and plateau is characteristic of constrictive pericarditis or amyloidosis or left heart failure. But once again, before one can be sure it is not heart failure, one must see how high the plateau is; and that we do not know. In constrictive pericarditis, as the right ventricle expels the blood, it cannot distend and, therefore, even though the first curve is high, it goes down and quickly goes up again, but how high does it go? They used the term "M-shaped," which means 2 positive plateaus in the atrium of about the same height that do not go down to the base line because the atrium cannot empty itself. This could be a good sign of constrictive pericarditis or amyloidosis or very unusual fibroelastosis, which occurs even in adults and involves both sides of the heart. What about Ebstein's disease? This is a possibility. There appears to be some involvement of the tricuspid valve.

Cardiac operation was performed on May 16, 1953. We could speculate that the preoperative diagnosis was either mitral stenosis or constrictive pericarditis. They would not have operated for Ebstein's disease or amyloidosis. Venous pressure preoperatively was 33 cm. of saline; postoperatively, 27 cm. of saline. There was only slight improvement postoperatively; the patient required monthly abdominal paracentesis, weekly mercurial injections, and he was maintained on a low-salt diet, digitalis, and ammonium chloride. He was forced to stop work in November 1953, but was able to remain ambulatory at home. Since there was no improvement following operation, this probably was neither mitral stenosis nor constrictive pericarditis.

On the day prior to admission to Cook County Hospital, the patient noted sudden onset of increased abdominal distention, severe dyspnea, and marked weakness. The amputation stump became very red. On the day of admission he was noted to be very blue and became incoherent. Abdominal paracentesis was performed, and the patient was referred for hospitalization.

Systemic review revealed only nocturia, several times, for 2 years, but on the day prior to admission the patient seemed to pass no urine.

Past history revealed only appendectomy. Venereal disease was denied. There was no known rheumatic fever or chorea in childhood.

Family History. One older brother had died of a heart attack and 1 of cancer of the liver.

Social History. The patient drank only socially and smoked 10 to 20 cigarettes a day.

Physical examination revealed a well developed, moderately well nourished, apprehensive, young white man with labored respirations and marked cyanosis. His blood pressure was 82/58 mm. Hg, pulse 112 and regular, respirations 32/min. and temperature 101 F. His head, eyes, fundi, ears, nose, mouth, and pharynx were negative, apart from cyanosis. There were no petechiae. Neck veins were slightly distended. Dullness and decreased breath sounds were noted over the right lung base posteriorly; coarse rales were heard at the left posterior lung base. A well healed left thoracotomy scar was present. The cardiac apex beat was palpable in the left fifth intercostal space in the midclavicular line, which means it was not much enlarged. No thrills were felt, and no murmurs were heard. What happened to those murmurs? In the state of shock one may not hear murmurs.

A firm liver edge was palpable 3 fingerbreadths below the costal margin. The spleen was not felt. The abdomen was soft, and dullness was noted in both flanks. The paracentesis site was draining serous fluid. The femoral pulse was palpable on the left but not on the right; therefore, the thrombosis was high. It involved not only the right common femoral but the right common iliac. The right amputation stump was markedly erythematous, warm, and tender. The nailbeds were deeply cyanotic. There was a questionable left Babinski sign, but superficial neurologic examination was otherwise negative.

Laboratory data. Urinalysis: Specific gravity 1.015; acid; albumin 4 plus; no sugar, acetone;

sediment negative. Hemogram: Hemoglobin 88 per cent; leukocytes 21,250; platelets adequate; polymorphonuclear cells 40, band forms 53, lymphocytes 3, monocytes 4; marked toxicity; Doehle bodies; rouleaux and burr cells. Blood culture revealed no growth.

Electrocardiogram showed moderately low voltage and isoelectric to slightly inverted T waves in standard and limb leads.

Hospital Course. The patient was treated with morphine, mercuhydrin, oxygen, penicillin (2.4 million units/day), streptomycin (1 Gm./day), digitalis, ammonium chloride, low-salt diet, and norepinephrine. Shock persisted although cyanosis subsided and sensorium cleared. On the second day, 350 ml. of concentrated urine was obtained by catheterization. On the third day, blood pressure remained at levels of 60–70/42–44, despite increasing amounts of norepinephrine. Urinary output was noted to be less than 50 ml./24 hours. Temperature remained elevated to 101 F. Increasing pulmonary rales and abdominal distention were noted. The patient was given 100 mg. of cortisone intramuscularly. His general condition remained poor, and he died 53 hours after admission, following a total duration of illness of 3 years.

There was nothing very unusual in the hospital course. The patient had a very low pressure and was in shock. Why? Because he developed pulmonary infarcts or embolism. Perhaps he even had a large thrombus in the atria, a ball-valve type of thrombus.

If this man did not have congenital heart disease, I would say primary amyloidosis would explain everything: intractable heart failure, cardiac murmurs, and the findings at catheterization. The only point that bothers me is, could the embolus be the first manifestation of amyloidosis? Possibly. The second diagnosis I would think of is constrictive pericarditis.

Dr. Hans Popper: Can we show you the operative findings now?

Dr. Gasul: Yes. The report informs us that the lungs appeared normal; there was no pleural effusion; 200 ml. of clear fluid was removed. The heart was rotated and the right ventricle was very muscular. Systolic contractions were normal. Systolic thrills were present over the pulmonary artery and the posterior surface of the heart. The pulmonary pressure was very low, but that can be very misleading because there does not have to be a stenosis. The pulmonary artery pressure was normal previously, so that perhaps he had a pulmonary stenosis with embolism from a congenital heart; but there is no evidence of that on the electrocardiogram or on the x-ray films or from the heart sounds. I would expect the pulmonary second sound to be absent or diminished. The left atrium was enlarged but neither atrium appeared to be under increased pressure. There was no evidence of mitral stenosis. The right ventricle appeared abnormally formed. There was a long pulmonary infundibular stenosis. The pulmonary valve could not be reached because of thickening of the ventricular wall. By means of force the infundibular stenosis was incised.

Now that changes things but the information is very misleading. I cannot see how anyone can have infundibular stenosis without high pressure in the right ventricle, and with an electrocardiogram of this kind, unless there are associated lesions decreasing the pressure in the right ventricle. Ebstein's disease is still a possibility; it could have gone on for 36 years, with paradoxical embolism having occurred through a patent foramen ovale. I believe that there are definite evidences of involvement of the tricuspid valve by a downward displacement and malformation of the valve.

Dr. A. B. Rimmerman: All the way through you have spoken of amyloidosis. Was that in anticipation? You have no evidence for it.

Dr. Gasul: Intractable heart failure and the findings at catheterization suggest amyloidosis. The only thing that disturbs me is the embolus as the first manifestation.

Dr. L. Feldman: I wish I had not heard the operative report. I thought at first that there could be a patent foramen ovale without right heart strain, but it would be unlikely to have a paradoxical embolus in such a condition. However, he could have had Concato's disease, which is a polyserositis, and also a paradoxical embolus occurring during a transient increase in right atrial pressure.

Dr. Jacob W. Fischer: I think the electro-

cardiogram is suggestive of right ventricular hypertrophy. The T waves in leads II and III are inverted and asymmetric. The S-T sectors in these leads are depressed. While this pattern is not pathognomonic of right ventricular hypertrophy, it is, however, suggestive. Of course, if the patient was taking digitalis, the S-T and T changes may in part be attributed to this drug.

DR. GASUL: I also thought of Concato's disease but that term does not mean anything. What is Concato's disease? It is not a disease. It is a polyserositis that can be due to a number of things. I considered paradoxical embolus but there has to be a cause for the increased pressure in the right atrium. I do not believe that there is any evidence of either atrial or ventricular septal defects. A congenital involvement of the tricuspid valve appears very probable.

PATHOLOGIC OBSERVATIONS

DR. POPPER: At necropsy the body was edematous. The iliac artery was occluded by a thrombus extending to the amputation stump. The arterial wall showed moderate atherosclerosis similar to that in the aorta. The kidney was severely congested as evidenced by proteinuria and hyperemia of the vessels at the corticomedullary junction. The gastrointestinal tract also was congested. The veins in the gastric cardia and in the esophagus showed varicose dilatation. The serosa of the gastrointestinal tract was diffusely thickened, as a result of chronic fibroplastic inflammation, in keeping with ascites (500 ml.). Considerable ascitic fluid was also found at necropsy. The spleen was very large (630 Gm.). Its thick capsule was hyalinized. Histologically, there was evidence of portal hypertension and recent reactive hyperplasia.

A section of the liver biopsy specimen, obtained at operation 1½ years before death, showed moderate passive congestion, the architecture being rather well preserved. The liver at necropsy was not significantly enlarged (1600 Gm.). Its capsule also was very thick, gray-white, and hyalinized, resembling a sugar-icing, as is seen in chronic ascites. The lobular architecture on the cut surface was obscured by a severe chronic passive congestion. The wall of the central and sublobular veins was very thick, due to fibrosis, and newly formed elastic membranes were noted, all caused by increased venous pressure. The central lobular zones showed either severe congestion and necrosis or fibrosis, and connective tissue septa extended bridgelike from one central field to the next, reversing the lobular architecture. These are the changes referred to as cardiac fibrosis of the liver. In many lobules, however, the septa extended from the central to the portal canals. The lobular architecture was destroyed and regenerative nodules formed; the picture of a true cirrhosis was thus produced. This is one of the rare specimens of true cardiac cirrhosis that we have observed. It develops in only 2 instances: chronic pericarditis and tricuspid incompetence.

There was right pleural effusion (800 ml.) and obliterating left pleural adhesions. Acute pulmonary congestion was not accompanied by evidence of prolonged pulmonary hypertension. Emboli were present in the right pulmonary artery.

The heart weighed 400 Gm. There were extensive, but loose, pericardial adhesions. The right atrium was very large and dilated. Its septum was intact and the foramen ovale closed. Fairly recent thrombi in organization completely filled the right atrium. The tricuspid valve appeared stenosed, measured 9 cm. in diameter and failed to admit 2 fingers (fig. 3*A*). When the value was opened, the cusps, however, were not significantly altered, and the chordae tendineae were delicate (fig. 3*B*). No muscular portion of the right ventricle was noted above the tricuspid stenosis. This excludes Ebstein's malformation, which consists of a pulling down or falling down of the tricuspid valve and a division of the right ventricular cavity rather than a separation of right atrium from right ventricle.[1] The tricuspid ring was thickened and scarred (fig. 3*B*). The stenosis was thus produced by changes in the tricuspid valve ring. Histologically, the connective tissue of the valve ring was a loose, in places almost an embryonal connective tissue, indicating the congenital character of the tricuspid stenosis. An elastic layer separated

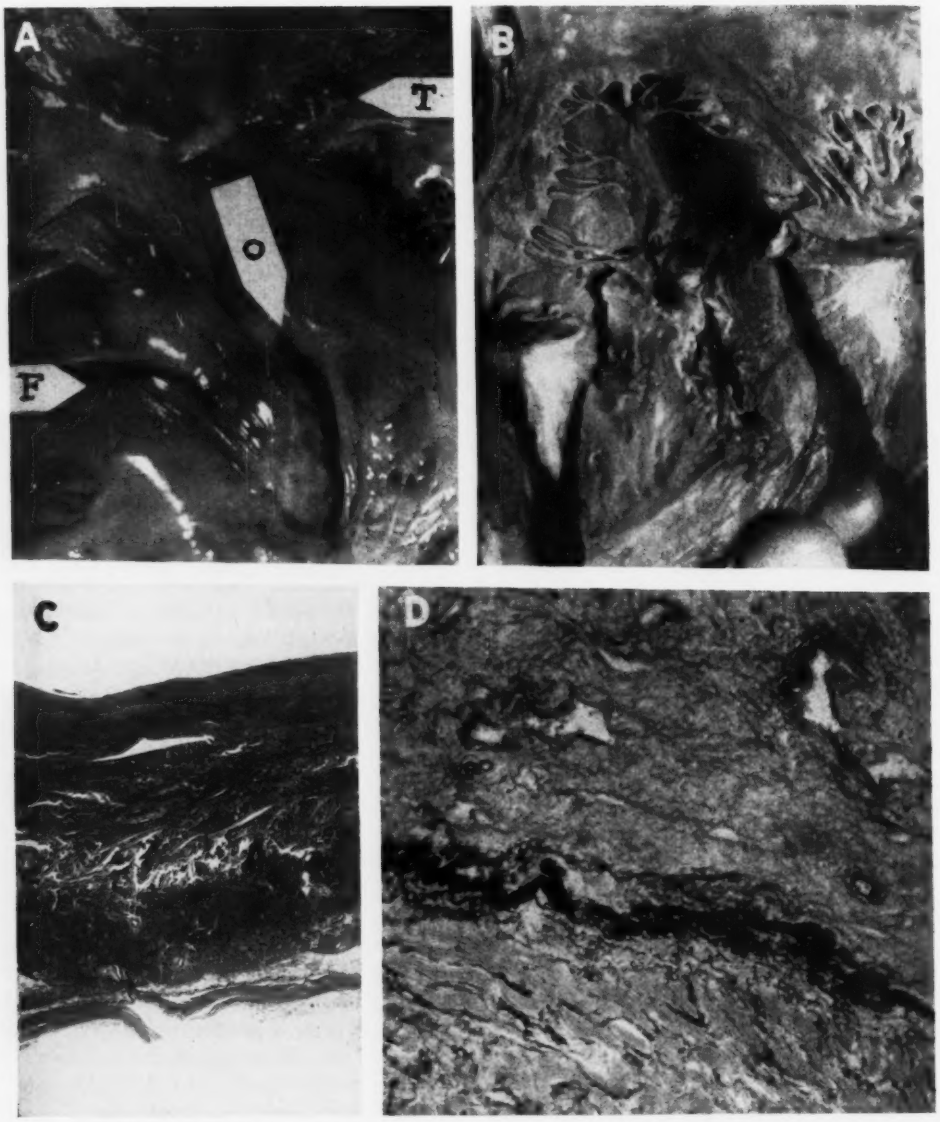

FIG. 3. *A*. Dilated right atrium with closed foramen ovale (*F*), organized thrombi in right appendix (*T*), and fishmouth stenosis of tricuspid orifice (*O*). *B*. Tricuspid orifice exposed by incision of the markedly fibrosed ring. The cusps and chordae tendineae are normal. *C*. Section through fibrosed myocardium of atrophic inflow tract of right ventricle, with markedly thickened endocardium, above, and pericardial fibrous adhesions, below. (3×, Mallory aniline blue stain.) *D*. Border between endocardium and myocardium in atrophic inflow tract of right ventricle, indicated by reduplicated elastic membrane. Sparser elastic membranes and vessels in thickened endocardium. (150×, orcein stain.)

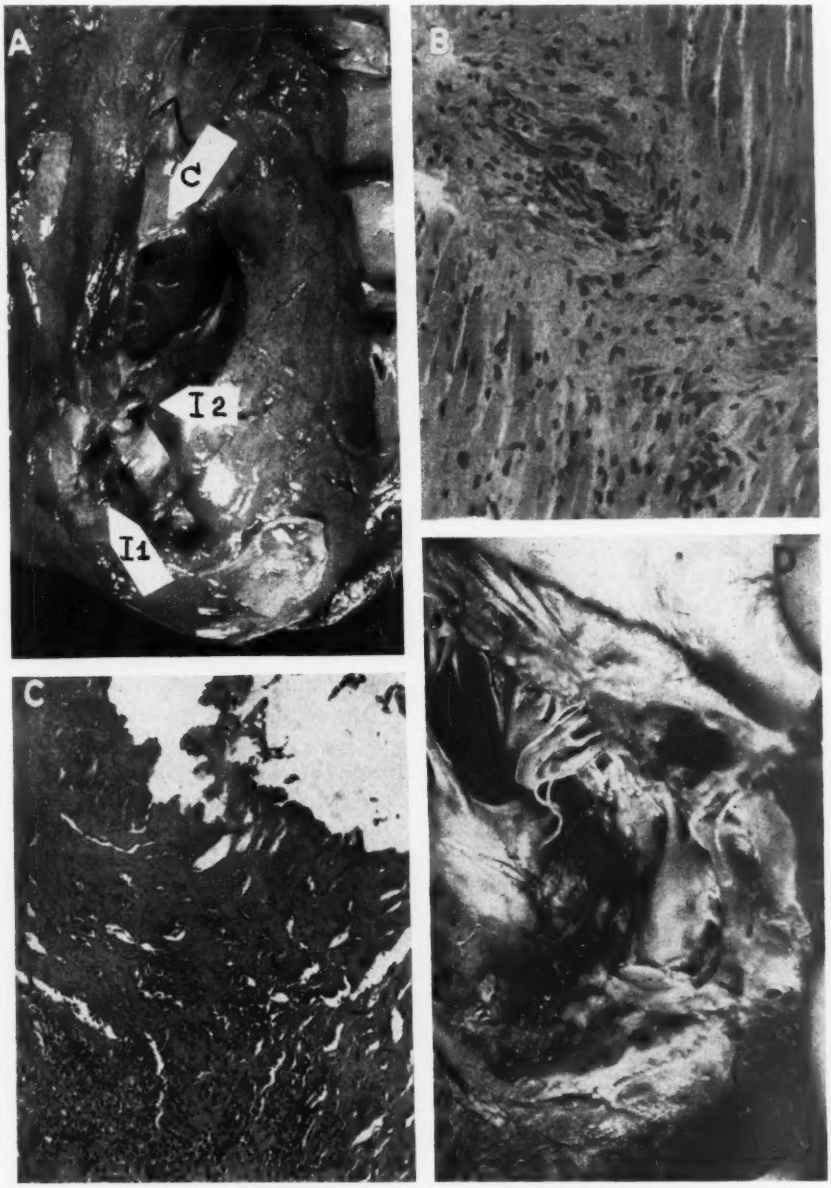

FIG. 4. *A*. Atrophic inflow tract of right ventricle forms a small appendix (between arrows I_1 and I_2) with thickened endocardium and fibrosed myocardium. Tricuspid ostium leads directly into widened pulmonary conus (*C*). The supraventricular crista (below arrow *C*) lies between conus and ostium. The pulmonary valve is normal. *B*. Periarterial fibrosis and cellular infiltration in myocardium of left ventricle (fibrosing Aschoff body). (135×, hematoxylin and eosin stain.) *C*. Subacute bacterial endocarditis with fibrinoid degeneration and leukocytic infiltration of the valve. (13.5×, periodic acid-Schiff reaction.) *D*. Mild, rheumatic fibroblastic deformity of mitral valve, and vegetative endocarditis of posterior leaflet of mitral valve. Mural thrombi at apex.

this connective tissue from the myocardium and seems to represent the original endocardium (fig. 3*D*). Moreover, in the connective tissue, elastic membranes arranged like a collapsed sac suggested a fetal endothelial-lined canal, possibly representing a rudimentary chamber. It appears, thus, that in this instance the endothelial cushion that normally separates right atrium and ventricle and gives rise to the tricuspid valve is disorganized. This results in excessive connective tissue with irregular formation of elastic membranes, narrowing of the ring, and tricuspid stenosis. The lesion may be included in the group of fibroelastosis. The tricuspid ostium led into a small blind sac, measuring 1 by 4 cm. and lined by thickened endocardium, surrounded by a very thick, fibrosed muscular wall (fig. 3*C*). This blind sac represents the hypoplastic inflow tract, or sinus, of the right ventricle. Apparently this area was incised during operation, and this may have contributed to the fibrosis. However, the endocardium here also showed excessive numbers of elastic membranes that doubtless are independent of the operation. The wall of the right ventricle showed diffuse myocardial fibrosis (fig. 3*C*). The tip of the blind sac contained mural thrombi in organization.

The pathway of egress of blood from the right ventricle remained a problem. The clinical assumption was made that an infundibular stenosis was present. Therefore, the pulmonary artery was opened; it appeared normal, as were the pulmonary cusps. The infundibular portion of the right ventricle, over which a metal clip indicated a surgical incision, was surprisingly dilated rather than stenosed. This infundibular area had a normal smooth wall. It extended to the supraventricular crista, which normally separates the smooth outflow tract from the inflow tract normally lined by trabeculae carneae.[2, 3] In this instance, the crista was close to the tricuspid ostium and except for the blind sac, hardly any inflow tract existed (fig. 4*A*). We deal, therefore, with a hypoplasia of the right inflow tract, with fibroelastosis. The blood flowed through the stenotic tricuspid valve directly into the infundibular portion. This is compatible with the physical findings as well as the catheterization data.

The left atrium was markedly dilated. The left ventricle was hypertrophic and dilated. Its wall was fibrosed, and the thickened endocardium of the apex was covered by organizing mural thrombi. Microscopic examination of the myocardium revealed diffuse myofibrosis in addition to periarterial scars derived from fibrosing Aschoff nodules (fig. 4*B*). The rheumatic disease of the left ventricle was confirmed by valvular changes. In contrast to the changes at the tricuspid ostium, where the valve was free but the ring altered, the valve cusps themselves were the seat of disease. Thick irregular adhesions deformed the commissures of the aortic valve. Histologically, the cusps appeared fibrosed and vascularized. This fibroblastic deformity was probably not marked enough to produce murmurs or circulatory disturbance. The chordae tendineae of the mitral valve were thickened and matted together. The mitral valve leaflets were scarred on the free edge at the line of closure, producing a rheumatic mitral stenosis. On the atrial surface of the posterior leaflet there was an irregular ulcerated area more than 1 cm. in diameter (fig. 4*D*). It was in part covered by irregular vegetations, some of which were calcified. Histologically, fibrinoid degeneration of the valvular tissue produced irregular vegetations, and infiltration by histocytes, lymphocytes, and especially segmented leukocytes, confirmed the diagnosis of a subacute bacterial endocarditis (fig. 4*C*).

Clinical Pathologic Correlation

Dr. Popper: This patient had a congenital tricuspid stenosis caused by a disorganization of the cushion separating atrium and ventricle.[4] In addition, he had a hypoplasia and deformity of the pulmonary sinus. Both are an expression of fibroelastosis, which is now considered to be a disturbance of the organization of the endocardial lining in prenatal life.[5-7] This congenital lesion accounted for the demonstrated high right atrial pressure associated with low pressure in the right ventricle and pulmonary artery but probably caused little functional impairment.[8] A rheumatic lesion in the left heart with mild fibroblastic deformity of aortic and mitral valve and myo

fibrosis led to mural thrombi in the left ventricle and embolism into the right leg, the first clinical sign, 3 years before death. Now the minimal functional disturbance attributable to the congenital lesion in the right heart was aggravated by the rheumatic lesion. Cyanosis and dyspnea appeared, the venous pressure and the circulation time increased, and edema and ascites developed. The murmurs heard may have been caused by both right and left-sided valvular lesions. The operation 1½ years before death did not improve the condition but possibly increased the cardiac fibrosis, especially of the right ventricular wall, and caused pericardial adhesions. Both led to increased hepatic congestion and, as a comparison with the liver biopsy demonstrated, only now true cardiac cirrhosis developed with the characteristic hyaline perihepatitis and perisplenitis. Terminally, a subacute bacterial endocarditis developed in the mitral valve that was damaged by the preceding rheumatic valvulitis. It was reflected in the leukocytosis, fever, and splenomegaly, and was the ultimate cause of death.

Final Pathologic Diagnoses

Fibroelastosis with congenital tricuspid stenosis; hypoplasia of right ventricular inflow tract; myocardial fibrosis and mural thrombosis; rheumatic myocarditis; aortic and mitral valvulitis with mitral stenosis; chronic passive congestion of viscera; cardiac cirrhosis; and terminal subacute bacterial endocarditis.

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Thus history teaches us that any division of the science and the art of medicine is necessarily harmful to practice. The physician of today, better realizing the limitations of bacteriological and other technical aids, is experiencing the need of returning to the patient's bedside, from which medicine should never have separated itself.—Arturo Castiglioni, 1874.

CLINICAL PROGRESS

Differential Diagnosis of Angina Pectoris

By JOSEPH E. F. RISEMAN, M.D.

IN MOST instances, the diagnosis of angina pectoris can be made with comparative ease and assurance; however, in a small percentage of cases diagnosis is very difficult. Because of the far reaching prognostic and therapeutic implications of the diagnosis, these latter cases assume an importance far out of proportion to their actual frequency.

The difficulties in diagnosis occur because, up to the present time, objective tests are not available to determine whether attacks of pain are of cardiac origin. Now, as in Heberden's time, the diagnosis rests on the patient's ability to describe his symptoms and the physician's ability to evaluate the patient's description. In practice, difficulties in diagnosis arise from inability to obtain a clear-cut, dependable history, and lack of general agreement or lack of knowledge as to what should be included in the term angina pectoris. It is therefore advisable first to define the terms that are currently used, and to discuss the relationship of angina pectoris to other manifestations of coronary heart disease.

NOMENCLATURE AND INTERRELATIONSHIPS

Angina pectoris is a term applied by Heberden in 1768[1] to a group of symptoms consisting of short attacks of anterior chest discomfort, usually precipitated by exertion. According to present concepts, these attacks are due to temporary anoxia or ischemia of the myocardium which results when the coronary circulation is inadequate for the needs of the myocardium at that moment. The inadequacy of the circulation generally is due to abnormality of the coronary arteries, usually arteriosclerosis.

Angina pectoris is not a specific disease, but rather a symptom complex that constitutes a clinical entity with a characteristic clinical course. Incapacity for heavy exertion is a universal finding, and sudden death or myocardial infarction are the most common complications.

The terms "angina of effort," "angina decubitus," and "status anginosus" are used frequently but are often more confusing than helpful. They do not imply different types of angina pectoris, but rather different clinical conditions under which attacks may occur.

The frequency with which angina pectoris is associated with coronary artery sclerosis has resulted, unfortunately, in the interchangeable use of the terms "angina pectoris," "coronary artery disease," "arteriosclerotic heart disease," "coronary heart disease," and "coronary insufficiency." These terms are not synonymous; to prevent confusion they should be limited to their original or basic meaning.

Coronary artery disease indicates pathology of the coronary arteries. Arteriosclerosis is most frequently responsible, but other conditions, such as encroachment on coronary arteries by tumors and syphilis, distortion of the aortic valves, certain rare forms of arterial disease such as Buerger's or Raynaud's disease, embolism, and even prolonged hypotension due to shock, may result in poor coronary circulation (fig. 1).

Coronary artery disease does not always result in symptoms or signs of cardiac involvement (fig. 2). For example, the onset of angina pectoris, myocardial infarction, or unexpected cardiac death usually occurs on the basis of pre-existent coronary artery pathology, even though previous examination by electrocardiogram or any other clinical tests may have been normal. Postmortem studies show that unsuspected coronary artery disease is not uncommon.

Arteriosclerotic heart disease means cardiac

From the Department of Medicine, Harvard Medical School, and the Medical Research Department, Beth Israel Hospital, Boston, Mass.

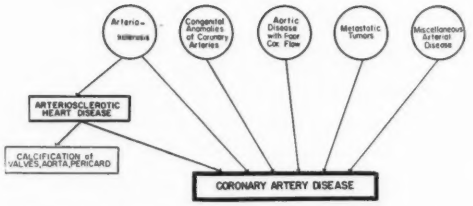

FIG. 1. Causes of coronary artery disease or poor coronary blood flow.

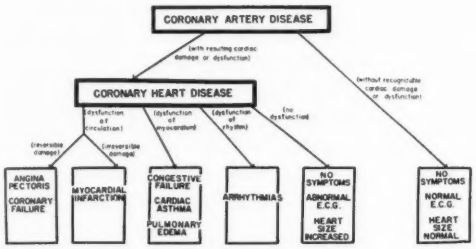

FIG. 2. Clinical manifestations of coronary artery disease.

damage or disturbance of function due to arteriosclerosis of the coronary arteries, aorta, endocardium, or pericardium (fig. 1).

Coronary heart disease means cardiac damage by impaired nutrition from coronary artery disease (fig. 2). The disturbance of function may be evidenced by pain, congestive failure, arrhythmias, etc. Anatomic damage may be demonstrated by abnormalities of the electrocardiogram or heart shadow but such findings are not necessarily accompanied by cardiac symptoms.

Coronary insufficiency is, basically, a physiologic term implying insufficient coronary circulation for the needs of the myocardium. This discrepancy between supply and demand may follow effort, coronary spasm (if it occurs), fall in blood pressure, abnormal rhythms, and coronary occlusion. Unfortunately, the term coronary insufficiency has been used to indicate not only the physiologic discrepancy between supply and demand, but also the many clinical results of this mechanism, namely, angina pectoris, coronary failure, myocardial infarction, cardiac asthma, pulmonary edema, arrhythmias, and both temporary and permanent electrocardiographic abnormalities. It would seem advisable to limit the use of the term coronary insufficiency to its physiologic meaning.

If the myocardial anoxia or ischemia resulting from coronary insufficiency is prolonged and severe, permanent anatomic changes may occur, i.e., myocardial infarction. If coronary insufficiency is short in duration, pain, dyspnea, or electrocardiographic changes may result; however, with readjustment of the balance between supply and demand, the abnormal symptoms and signs disappear and no permanent myocardial damage results. The short episodes of chest pain are *angina pectoris*.

The term *coronary failure* denotes a syndrome intermediate between angina pectoris and myocardial infarction. Physiologically it is due to anoxia or ischemia that is prolonged but does not result in irreversible changes in the myocardium. Clinically it is characterized by chest pain more prolonged than angina pectoris and often accompanied or replaced by disturbed cardiac function (such as cardiac asthma or arrhythmias) but not resulting in evidence of permanent myocardial damage, i.e., without fever, leukocytosis, or progressive electrocardiographic changes.

Angina pectoris is only one of the manifestations of coronary artery disease. Angina pectoris is usually caused by coronary arteriosclerosis; however, there are other causes (fig. 3).

There is a small but important group of patients in whom angina pectoris is precipitated by thyrotoxicosis, polycythemia vera, anemia, or abnormal rhythms. It is probable that these patients have underlying coronary arteriosclerosis. The impaired coronary circulation in these patients appears adequate under usual conditions but becomes inadequate for the needs of the heart when the demands are increased by thyrotoxicosis, the supply is decreased by arrhythmias, or the delivery of oxygen is impaired by anemia or polycythemia.

Another small group with coronary artery disease and angina pectoris, but without coronary arteriosclerosis, includes patients with metastatic tumors surrounding the coronary arteries, congenital malformations of the coronary vessels, and Raynaud's disease or

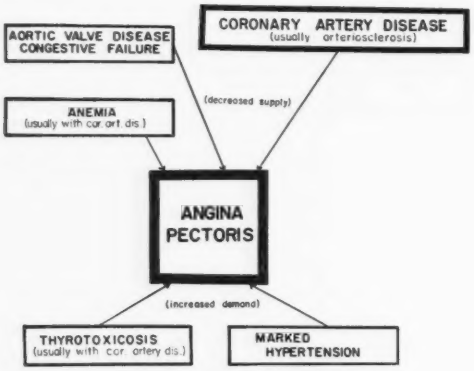

FIG. 3. Cause of angina pectoris

thromboangiitis obliterans involving the coronary tree.

On the other hand, angina pectoris may occur in the absence of coronary artery disease. For example, a few patients with severe arterial hypertension have angina pectoris, yet show little coronary arteriosclerosis post mortem.

Similarly, congestive failure or aortic valvular disease may result in poor coronary blood flow, myocardial anoxia, and angina pectoris.

Finally, there is an important group of patients with symptoms suggesting angina pectoris in whom it is difficult to establish the diagnosis with certainty. In such instances, the terms "pseudo angina" or "atypical angina" are frequently used, and both the patient and the doctor may worry for years about the possibility of coronary artery disease. In most instances, however, a careful history and examination will separate these cases of "atypical angina" into those with typical angina and those who definitely do not have angina pectoris. A small but important group remains, however, in whom the diagnosis remains in doubt, even after careful study.

THE DIAGNOSIS

Heberden's original (1768)[1] 1-sentence description has not been improved upon for simplicity and clarity. "*They who are afflicted with it are seized while they are walking, (more especially if it be up hill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all this uneasiness vanishes.*"

One hundred and forty years later (1910) Osler[2] pointed out that little had been added to this description. Both of these master clinicians, however, included under angina pectoris other related or somewhat similar conditions such as myocardial infarction, "spasmodic disorders," and cardiac neuroses. A more recent analysis (1937) of the histories of 100 patients whose angina pectoris was confirmed by observation during typical attacks showed 5 characteristics in common.[3] These 5 diagnostic criteria, which are implied in Heberden's original description, serve as a valuable yardstick for the diagnosis of angina pectoris: *S*udden onset, *A*nterior chest, *V*ague discomfort, *E*xertion precipitates, *S*hort duration = *SAVES*.

The diagnosis of angina pectoris depends on adequate history taking. The examiner should record the specific description given by the patient, not what he thinks the patient is trying to say (except in summary). A few well directed questions will usually fill in the gaps and clarify the picture, but leading questions should be avoided. At first the patient may not notice details such as the exact location or the duration of the pain; however, such questioning leads to more careful observation so that a much more detailed and accurate account can subsequently be obtained.

1. *Angina is sudden in onset*, the attack develops within a few seconds and, as has often been pointed out, between attacks the patient is perfectly comfortable. The patient who states, "I felt it coming on all morning," or "it gradually increased in intensity over hours," is not talking about angina.

2. *The discomfort is in the anterior part of the chest.* This area lies between the anterior axillary lines on the sides, the epigastrium below, and the suprasternal notch above. "Retrosternal" is a term that is used more often by physicians than by patients. Unfortunately this term is used too loosely to be of diagnostic value. The pain is most commonly located under the upper

or mid portion of the breastbone but not always. It is least commonly felt at the cardiac apex; discomfort limited to the region under the left breast should be viewed with suspicion. Similarly, pain in the region of the mid or posterior axillary line is probably not angina. Patients may have pain in the upper thoracic back, but this is usually overshadowed by the discomfort in the anterior aspect of the chest.

Radiation is important, but occurs in only about 60 per cent of cases, most commonly to the *inner aspect of the arm*, especially the left arm. Pain in the outer aspect of the arm is likely to be due to disease of the cervical spine.

3. *The discomfort is vague and difficult to describe exactly.* It is painful but not necessarily described as pain. "Pressing," "squeezing," "choking" are terms commonly used. Often it will be described in relation to the patient's work or experience. For example, a real estate dealer described his attacks as "the Woolworth Building sitting on my chest," while a cowboy described a "branding iron in my chest and a lariat around my throat." The discomfort is different from pins and needles, and it is not shortness of breath, although this may also be present.

4. *The attacks are precipitated by exertion.* The relation to exertion is one of the most helpful points in diagnosis. Patients may also have angina on emotion, it may be more frequent in the cold, it may occur while at rest, after meals, or during sleep, but if the patient is asked "what brings on an attack," the usual answer is that he gets it "when walking out of doors." The patient who has angina after meals is more likely to have it on walking after meals than while sitting quietly at the table.

Cases with angina on emotion but not on exertion exist, but they are very rare. In such cases it is advisable to find out how much the patient walks, for it may be discovered that he walks slowly and as little as possible. If the patient states that he never gets attacks except when excited, ask "what would happen if you ran after a street car?" The answer probably will be, "I wouldn't dare do that for I'm sure I would have an attack."

5. *The attacks are short in duration.* Attacks measured with a stop watch, are practically always less than 3 minutes in duration. Few patients, however, except doctors with angina, measure their attacks. Most patients will state that the attacks are "short," "not long," "a few minutes," "5 minutes," or "less than 15 minutes" in duration. Doctors with angina frequently state that their attacks last "1 minute by my watch." Occasional attacks may last longer but be suspicious if the attacks *always* last an hour or more.

The patient with angina pectoris usually *has all 5* of these characteristics.[3] If 1 of these criteria is definitely absent, the patient probably does not have angina and another cause for the symptoms must be sought. A sixth important characteristic is the uniform pattern of the attacks in any given patient; although some variations may occur, they are usually slight.

The response to nitroglycerin may be helpful in diagnosis, but is often misleading. Many patients with angina pectoris are not benefitted by nitroglycerin while patients with gallbladder disease or psychoneurosis may obtain relief.

Physical and Laboratory Methods. Physical examination and laboratory studies are of little value in the diagnosis of angina pectoris. At best they indicate a condition which *may* result in cardiac symptoms. About one half of the patients have cardiac enlargement. About one-third have blood pressures lower than 140/90; another third have pressures of 150 to 160 over 90 to 100; and the remaining one-third have blood pressures of 165/100 or higher.[3] About one half to three fourths of patients with angina pectoris have abnormal electrocardiograms.[4] It is important to realize that in about one fifth of all patients with definite angina pectoris, the heart size, blood pressure and 12-lead electrocardiograms are normal.[4] In brief, the absence of objective signs of heart damage does not exclude angina pectoris, while the presence of such signs is not diagnostic.

Angina pectoris is infrequent in women under 45 without hypertension or diabetes, but it does occur.

Difficulties in Establishing the Diagnosis

Problems of Nomenclature. Some of the confusion about angina is due to indiscriminate use of terms that are not interchangeable. Coronary arteriosclerosis, coronary artery disease, arteriosclerotic heart disease or coronary insufficiency does not mean that the patient necessarily has angina pectoris.

Problems in Obtaining an Adequate History. Inadequate history taking is a common cause of difficulty in diagnosis. This is illustrated by group of 108 patients, diagnosed as having angina pectoris, who were recently re-evaluated in preparation for therapeutic studies.[5, 6]

In 73 of these patients (67 per cent), the history showed the typical 5 characteristics discussed above. In 63 of these 73, typical attacks were induced and observed during Standardized Exercise Tolerance Tests (described below under Objective Tests). The remaining 10 were apparently in a period of remission of symptoms for, although they had had typical angina in the past, no attacks had been experienced for months.

In the remaining 35 patients (33 per cent) the history was variable and distinctly different from that described above; furthermore, in none of these was it possible to induce angina by exercise under the standardized conditions. In 5 of these patients the pain was gradual in onset; these patients could feel it coming on or developing for hours before the attack developed. In 6 patients the pain was not in the anterior chest but in the abdomen, or in the extremities or in the head. In 23 it was not vague, but very definite in character; 8 described it as "shortness of breath" or "difficulty in breathing;" 7 as "pins and needles," 5 as "sharp" or "knifelike," and 3 as "heartburn" or "throbbing." In 21 it was not precipitated by exertion, but was either constant, or was brought on by deep breathing or occurred only on resting *after* exercise, or came only after meals or on damp days. In 11 patients the attack was not short in duration, but continued for hours or all day, while in 3 patients the discomfort was momentary only.

The sameness of the history in 73 of these cases and the marked variation of the histories in the other 35 is quite striking. If the histories were taken more carefully and more completely in the latter 35 patients it is questionable if a diagnosis of angina pectoris would have been made.

Table 1.—*Clinical Conditions Often Confused with Angina Pectoris*

System	Disease
Gastrointestinal	Abdominal angina
	Pancreatitis
	Esophageal disease
	Peptic ulcer*
	Hiatus hernia*
	Gallbladder disease†
Thoracic	Pleuritis
	Pulmonary infarction
	Spontaneous pneumothorax
	Herpes zoster
	Pulmonary or mediastinal tumors
Cardiac	Acute myocardial infarction
	Coronary failure*
	Arrhythmias
	Valvular heart disease*
	Congestive failure
	Dyspnea
	Pericarditis
Skeletal	Lower cervical or upper dorsal lesions
	Bursitis or "shoulder arm syndrome"
Nervous	Neuritis
	Psychoneurosis†
Miscellaneous	Thyrotoxicosis
	Anemia

* These conditions are confused frequently with angina pectoris.

† These conditions are confused very frequently with angina pectoris and their differentiation may prove especially difficult.

Language difficulty may present an insurmountable barrier. Interpretation by a member of the patient's family or a close friend rarely results in obtaining a clear description of the symptoms.

Phlegmatic or nonobservant patients may be unable to describe symptoms accurately. Fortunately such cases are not frequent.

Patients who are too observant may present a difficult diagnostic problem. In this category are those "neurotic patients" who are unable to overlook symptoms in other parts of the

body, and at other times of their life. Such cases are among the most difficult; they require all the care and judgment of the observer and often leave the diagnosis in doubt.

Angina Pectoris Simulating Other Disease. Angina pectoris may simulate "neuritis" if the discomfort in the arm is more prominent than the thoracic component. Similarly, angina may simulate gastric or gallbladder disease if the symptoms characteristically appear after meals. In such instances the repeated precipitation of discomfort in the arm or epigastrium with exercise of the legs, and also the short duration of the symptoms, may be helpful in diagnosis.

Noncardiac Conditions that Simulate Angina Pectoris. The list of conditions that may simulate angina pectoris is long and involves many organs (table 1), constituting the most frequently encountered problem in differential diagnosis.

Angina Pectoris Plus Some Other Disease. These patients often cannot separate one group of symptoms from the other. Careful review of such a history may differentiate 2 types of attacks, for example 1 type of pain that comes on exertion, and another type that comes after meals.

Specific Problems in Differential Diagnosis

For convenience, the many specific clinical conditions that may be confused with angina pectoris can be divided anatomically, as in table 1.

Gastrointestinal Complaints

Abdominal angina, if it exists, must be extremely rare. While arteriosclerosis of the mesenteric vessels undoubtedly exists and at times results in thrombosis, the clinical manifestations usually are those of acute abdominal disease, are not repeatedly induced by walking, and are likely to be prolonged.

Pancreatitis similarly may result in pain that is usually more than a few minutes in duration and is not characteristically, repeatedly brought on by normal exertion.

Esophageal disease such as spasm, ulceration, or diverticulosis may result in vague substernal discomfort, but this distress is usually related to food or the act of swallowing rather than to walking. Roentgen studies should establish the diagnosis.

Peptic ulcer is frequently confused with angina pectoris, especially in patients whose symptoms begin after 50 years of age, or in patients who describe their substernal discomfort as "heartburn." Careful history and x-ray studies differentiate the 2 conditions in most instances. There are, however, patients who suffer attacks of angina after eating; in such cases, a history of identical attacks brought on by exertion should establish the diagnosis.

Diaphragmatic hernia, presumably because the same nerve pathways are involved, may have the same localization and the same vague character as angina pectoris. Furthermore, both conditions may be episodic, with complete freedom from symptoms between attacks. The symptoms of diaphragmatic hernia, however, are likely to be precipitated by eating or assuming the recumbent position (rather than by exertion), and are more likely to be associated with other digestive disturbances such as vomiting or hematemesis. X-ray studies usually establish the presence or absence of diaphragmatic hernia, but angina pectoris may coexist.

Gallbladder disease is often confused with angina pectoris. In fact, it has been suggested that the 2 conditions are related and that gallbladder disease may lead to coronary artery disease or myocardial degeneration.

The frequent coexistence of gallbladder disease and angina pectoris can be explained by the fact that both occur in the same age group. Even though the patient may have definite evidence of gallbladder disease, any attacks of vague discomfort in the anterior chest precipitated by exertion and of short duration must be considered to be angina pectoris due to coronary artery disease.

Thoracic Disease

Noncardiac thoracic disease usually can be differentiated readily from angina pectoris. The pain of pleurisy or pleurodynia is usually lancinating and related to respiration. The pain of pulmonary infarction, spontaneous

pneumothorax, herpes zoster, or tumors of the chest wall or lungs is usually prolonged and does not occur in repeated identical attacks precipitated by walking.

Cardiac Conditions

Myocardial infarction can be differentiated by its prolonged duration, infrequency, signs of tissue damage, and characteristic electrocardiographic changes.

Coronary failure, may be difficult to differentiate except by careful observation over several days. Actually such episodes may be considered to be prolonged, severe attacks of angina pectoris. In most patients with angina, such episodes are sporadic rather than frequent.

Arrhythmias may be confused with angina pectoris. Premature beats may result in momentary episodes of vague anterior chest discomfort. If the extrasystoles are precipitated by exertion, the problem may be difficult. Careful history taking, however, should indicate that these episodes are less than a second, rather than minutes, in duration and may be described as "something turning over in the chest" or as "skipping." In other instances, observation while the patient is actually experiencing the symptoms will reveal their true nature. Prolonged arrhythmias, especially when the ventricular rate is rapid, may be accompanied by chest pain typical of angina pectoris except that it may occur spontaneously and persist for as long as the rapid rate continues. Diagnosis in these instances is usually not difficult, especially if the patient is observed during a typical attack.

Valvular heart disease, especially aortic valvular disease, may interfere with adequate coronary artery filling and result in angina pectoris. Physical examination usually clarifies the situation. In patients over 50, the coexistence of coronary arteriosclerosis must be considered.

Congestive failure frequently brings about episodes of vague anterior chest discomfort on slight exertion, e.g., mitral stenosis. This is probably due to relative anoxia of the myocardium and is, therefore, similar to angina pectoris, both physiologically and clinically. However, in the absence of coronary arteriosclerosis, this syndrome does not progress to acute myocardial infarction; furthermore, these symptoms are usually overshadowed by other cardiac symptoms and signs of congestive failure.

Dyspnea on exertion, due to early congestive failure, emphysema, asthma, or lack of physical fitness, may be confused with angina pectoris. A careful detailed history clarifies the problem.

Acute pericarditis has been confused with angina pectoris, but the prolonged nature of the pain, fever, signs of inflammation, the characteristic clinical course, and electrocardiogram clarify the situation.

Skeletal System

Spinal lesions, especially arthritis or tumors of the lower cervical or upper thoracic spine, may result in sudden attacks of anterior chest and arm pain, short in duration, and difficult to differentiate from angina pectoris. The pain is usually sharp, and brought on by motion of the head or thorax. Forceful flexion and rotation of the head and neck should be included as part of the physical examination of every patient suspected of having angina pectoris. In some instances the fact that the pain is located in the outer rather than the inner aspect of the arm may be the first clue that the condition is radiculitis rather than angina pectoris.

Bursitis or "shoulder arm syndrome" usually causes no diagnostic difficulty except in patients with recent myocardial infarction. In such cases both the patient and attending physician are likely to be sensitized to the occurrence of any pain in this region and confusion in diagnosis may result. Again the diagnosis is made by observing that the pain is induced by motion of the arm rather than exercise.

Nervous System

Peripheral neuritis is occasionally the diagnosis in patients with angina pectoris, when the twinges of discomfort in the arm overshadow the rest of the picture. Careful ques-

tioning will reveal that the arm pain is preceded or followed by pain in the anterior chest and that both are induced by exercise. Conversely, pain in the arm may be called angina pectoris unless a detailed history is obtained.

Psychoneurosis, used in its broadest sense, undoubtedly causes the greatest difficulty in diagnosis. Psychoneurosis is a poor term, for it includes not only patients with cardiac neuroses and patients with overawareness of all symptoms, but also many intelligent, emotionally stable persons who have been educated to the fact that heart disease is the greatest cause of death and incapacity. Such persons naturally want either to recognize the condition in its earliest stages or to be relieved of their justifiable anxiety.

In patients who are obviously neurotic, the question of additional organic illness arises. Although some complaints may be obviously functional, other symptoms may resemble angina pectoris. The problem is often complicated by disability compensation, a language problem, or coexistent gallbladder or gastrointestinal disease.

In this group, an objective test to differentiate between cardiac and noncardiac disease would be of greatest value. Observation of the patient during a typical attack usually helps to settle the diagnosis by enabling the examiner to determine accurately the location, the duration, and the precipitating cause of the symptoms. In clinical practice, however, such opportunities are rare.

In our experience, the diagnosis in this group of patients often is made only after prolonged observation. Repeated history taking, at widely separated intervals of time, may reveal a noncardiac cause for the symptoms, or may reveal a variability in symptoms inconsistent with angina pectoris, plus a persistently normal and unchanging electrocardiogram. Needless to say, the examiner must avoid indicating to the patient the difference between his symptoms and those typical of angina pectoris. Talking to other patients or reading popular or medical literature does not teach these patients to give a more typical history. This, however, might not be true of an intentional malingerer.

Miscellaneous

Thyrotoxicosis may initiate angina pectoris, and it may be cured, at least temporarily, by adequate therapy of thyrotoxicosis. The clinical picture is usually sufficiently suggestive to indicate the advisability of metabolism tests.

Anemia, like thyrotoxicosis, may precipitate angina, again, only in the older age group with coronary artery damage.

Objective Diagnostic Tests

An objective test of undoubted accuracy and direct clinical application would be helpful, especially in borderline cases. Such a test should have the following characteristics:

1. The results of the test must be directly applicable to the clinical diagnosis of angina pectoris.
2. The results must be reproducible.
3. The test should be positive in a high percentage of patients with angina pectoris, i.e., there must be few "false negative" responses.
4. The test must be negative in all or almost all patients who do not suffer attacks of angina pectoris, i.e., there must be few or no "false positive" tests.
5. The test must be without danger to the patient.

The ideal test of undoubted and universal clinical value has not yet been devised. The tests advocated to date have considerable value in the laboratory for studying angina pectoris, but they cannot be recommended for general office use. They can be divided into 2 general types: tests with direct clinical application including those that attempt to reproduce attacks of angina pectoris in patients suspected of having such symptoms; and tests with indirect clinical application.

Direct Tests

Adrenaline Test

The adrenalin test, which attempts to induce angina by the subcutaneous injection of epinephrine, is dangerous and therefore contraindicated.[7]

Standardized Exercise Tolerance Test

The Standardized Exercise Tolerance Test

has been used successfully by the author and his associates in the Beth Israel Hospital since 1932.[8] Attempts are made to induce attacks of angina pectoris by having the subject exercise by repeatedly mounting and descending a 2-step staircase either in a cold room, 45 to 55 F., or while holding an ice cube in one hand.[9] The test is considered positive when the patient is forced to stop exercise because of the onset of discomfort that is typical of angina pectoris and is identical with what he experiences in daily life. The test is confirmed by repetition. The Standardized Exercise Tolerance Test differs from the "Master's test"[10] in many respects, but especially in the fact that the former aims to induce typical attacks of angina pectoris in patients with such symptoms, while the latter aims to induce electrocardiographic changes that are not necessarily related to any cardiac symptoms.

Clinical Applicability. The test has direct clinical application because:

1. The conditions under which the attacks are induced are directly comparable to those responsible for the majority of attacks in daily life; a normal and familiar exercise, stair climbing, in the cold.

2. The attacks are identical with those experienced by the patient in daily life.

3. The characteristics of the attack can be more accurately evaluated by observation during such typical episodes. The examiner can observe the sudden onset (within 2 to 6 trips before being forced to stop). The location can be determined accurately by direct delineation on the patient's chest and arms while he is experiencing the discomfort. The short duration, usually less than 3 minutes, can be measured by a stop watch. The induction by exercise is self evident, and the character of the discomfort can be confirmed by direct questioning during the attack.

Reproducibility. Unless there has been a marked change in the patient's clinical condition, i.e., remission or exacerbation of attacks in daily life, typical attacks are invariably induced after comparable amounts of exercise when the conditions of the test are standardized by being performed: (a) in a cold environment, (b) at least 1 hour after a light meal, (c) on a day when the patient has experienced no recent attack, (d) when he has received no medication that might change the exercise tolerance, and (e) after the patient has become accustomed to the test. In fact, the reproducibility of attacks with comparable amounts of exercise under the standardized conditions not only serves to confirm the diagnostic value of the test, but also makes it possible to study the efficacy of treatment.

False Negative Tests. These are extremely rare. As discussed in the section on diagnosis, patients suspected of angina pectoris who failed to develop typical attacks under the standardized condition proved to have symptoms quite different from those characteristic of angina pectoris. No medical test is infallible, and undoubtedly false negative tests must occur, but unless the clinical history indicates a complete clinical remission of symptoms, these errors are very rare. During the past 23 years only 2 have been brought to our attention. One patient was a 40-year-old Polish refugee who had typical attacks whenever he heard of the German invasion of his homeland, but he did not develop attacks in the cold room or on walking through the snow. The other was a man approximately 50 years of age who had several attacks of peculiar discomfort every hour while lying in bed; he did not develop similar attacks on exercise in the cold room, but a typical myocardial infarction occurred within a few weeks after the test.

False Positive Tests. These are also rare, especially if the test is repeated in all doubtful cases, and clinical judgment is exercised. Some difficulty arises in patients with asthma or severe dyspnea, but examination and observation should serve to discover such patients. Undoubtedly a well informed deliberate malingerer could confuse the examiner but, to our knowledge, this has not occurred.

Safety. In view of the unpredictable course of patients with angina pectoris and the frequency of myocardial infarction, no studies in angina pectoris are completely safe. For this reason the Standardized Exercise Tolerance Test cannot be recommended as a routine office procedure. It has proven to be a useful

laboratory technic of direct clinical value in the diagnosis and therapy of angina pectoris. Experience during the past 23 years with over 10,000 tests in many hundreds of patients has resulted in untoward effects on 5 occasions. Two of these occurred during the first 2 years of our experience, during studies of the characteristics, limitations, and criteria of the test. The first patient lost his attacks following total thyroidectomy and was given large amounts of thyroid extract. After return of the basal metabolism to normal, attacks of angina pectoris recurred in daily life, but they were more severe and more frequent than preoperatively. The Standardized Exercise Tolerance Test at this time was followed by a severe attack with death a few minutes later. The second patient complained of generalized weakness and faintness rather than chest pain on exertion. The test was followed by one of his typical attacks of weakness and faintness from which he recovered within a half hour. Since that time the following precautions have been taken: the test is not done in a patient whose history suggests myocardial infarction, either impending or within the preceding 6 months; the test is never performed in a patient who complains of marked weakness or faintness on exertion; the first test in each patient is used to allay apprehension and to accustom the subject to the procedure, i.e., the patient is rarely permitted to perform more than 20 trips. The comparative safety of the test during the past 20 years is undoubtedly due in great measure to these precautions and, considering the nature of the condition, undoubtedly due, in some measure, to good fortune. Two of the 3 untoward effects in the last 20 years were in patients who had been treated with hypotensive drugs (octyl nitrite and reserpine). These patients developed severe hypotension, faintness, and perspiration a few minutes after the completion of the test; recovery was complete in both subjects within a half hour. The third patient developed transient ventricular tachycardia and collapse after 1 of many tests; recovery was complete and prompt.

Indirect Tests

These aim to induce electrocardiographic evidence of anoxia in patients whose tracings under normal conditions show no evidence of myocardial disease. Such tests are indirect, because a positive electrocardiographic result does not prove that the patient has cardiac symptoms or will develop cardiac symptoms in the future. Many different test conditions have been employed[11] to induce electrocardiographic changes. The "Master's test" currently used[10] has the advantage of simplicity of technic and considerable accumulated experience. Several characteristics of the test limit its usefulness.

Master's Test

The procedure consists of obtaining the 3 standard and 1 apical precordial leads while the patient is at rest. With the electrodes and cable still attached to the subject, but not to the machine, the patient then repeatedly mounts and descends a 2-step staircase 18 inches high. The duration of the exercise is 1½ minutes, the number of trips performed in this period of time is prescribed according to the sex, age, and weight of the subject. Immediately after exercise the cable is connected to the machine and short strips of the 4 leads are again obtained.

A positive result is indicated by the development of electrocardiographic evidence of anoxia or ischemia in 1 or more leads; most commonly the changes consist of S-T depression with or without a tendency to T wave inversion. If the test is negative, it can be repeated with the patient performing twice as many trips in twice the time.

Clinical Applicability. This must be considered from several points of view.

1. *Clinical significance of a positive test.* A positive test does not imply that the patient experiences the symptoms that we call angina pectoris. Electrocardiograms taken continuously during exercise in patients with severe angina pectoris may show no change even when the patient is forced to stop exercise because of an attack. In other patients, electrocardiographic changes appear shortly after

exercise begins, long before onset of pain, and do not coincide in duration with the attack.[11]

A positive test does not necessarily indicate the patient has pathology that might result in cardiac symptoms. At this time it is pertinent to point out that the control studies have been performed for the most part on subjects under the age of 45, while the vast majority of patients with clinical coronary artery disease are over 50 years of age. A control study of active, working, apparently healthy subjects over 50 years of age is necessary, together with observation for a sufficiently long period of time to determine the clinical significance of the positive results.

Unfortunately, the specific symptoms that we call angina pectoris and the more general condition called coronary artery disease have not been carefully differentiated in the literature. In order to study subjects with coronary artery disease, patients with angina pectoris were selected, but in the interpretation of the results it is intimated that subjects with positive tests either have symptoms or are iikely to develop symptoms.

2. *Clinical significance of a negative test.* It is generally agreed that a negative test does not prove that the patient is free from coronary artery disease. Many reports from several different clinics show that from 40 to 80 per cent of patients with undoubted angina pectoris may have negative single Master's tests.[12-14] The negative results with the double Master's test in patients with angina pectoris are apparently less frequent[15] but occurred in 61 per cent of patients with angina pectoris and normal electrocardiograms at rest.[12] Negative double tests have also been obtained in patients with active or impending myocardial infarction.[16]

3. *Technical considerations.* A positive or abnormal response may be evidenced by a change in the level of the S-T interval of as little as 0.5 mm. This is extremely difficult to measure accurately especially in a tracing with a shifting baseline. Study of continuous electrocardiograms shows considerable variation from complex to complex due to respiration, motion, and other factors. In our experience, it is necessary to average the measurements of at least 10 consecutive complexes in order to rely on the accuracy of the results. This requires a longer strip than taken by the usual technic.

The 3 standard and 1 apical precordial leads are not most suitable for observing the results. Although changes in rhythm or the duration of P-R or QRS should be evident in any lead, changes in S-T and T are most frequently evident and most striking in the unipolar right arm lead and the apical precordial lead. If a single lead were to be used, as would seem advisable, lead 4R, in which potentials in the right arm and in the apical lead are summated, would be more likely to demonstrate changes than any of the 4 leads currently employed.

4. *Theoretic considerations.* The tables describing the number of trips to be performed were originally used as a test of myocardial or circulatory efficiency and represent the amount of work that normal subjects could perform in 1½ minutes with a return of pulse and blood pressure to the resting level within 2 minutes after the cessation of exercise.[17] It is questionable if the amount of work that has proved useful in measuring myocardial efficiency is the same as that necessary to measure coronary sufficiency. In fact, the frequent necessity of doubling the work suggests that the prescribed amount of work has no sound physiologic basis in coronary artery disease.

In the published reports, the criteria distinguishing normal from abnormal responses differ depending on whether one uses as the upper limit of normal the maximum changes observed in normal persons[18] or if one uses the lower limit of abnormal, as changes commonly observed in patients with angina pectoris.[10] If the former is used, a large number of patients with angina pectoris will have negative tests. If the latter is used, it is probable that abnormal results might be obtained in some normal subjects. It is not surprising that considerable overlapping occurs. Muscular contraction is an anaerobic phenomenon, oxygen being used for recovery; muscular contraction in all subjects results in some degree of anoxia or local oxygen debt.

Reproducibility. Electrocardiograms taken continuously during and following exercise that induces angina pectoris show rapidly progressive changes. Immediately after the

cessation of exercise, within 15 seconds, S-T depression is most common and most striking; later, progressive T wave changes become more evident. In publications that show 2 or more complexes in each of the 4 leads, the heart rate is considerably slower in the leads obtained toward the end of the test. This change indicates that an appreciable amount of time must have elapsed between obtaining the earlier and the later leads, and, therefore, the results are not comparable. Furthermore, it would be extremely difficult to repeat the test and obtain each of the 4 leads at identical times in the 2 tests.

In addition to the technical difficulties described above, even slight shifting of the precordial electrode in relation to the heart during the test may result in S-T and T changes unrelated to anoxia.

These technical considerations make it difficult to reproduce identical results in a given patient. In order to get results that are reliable and comparable, it is necessary to use either a multichannel electrocardiograph or take only 1 lead at a definite time (preferably within 15 seconds) after the cessation of exertion.

False Negative Tests. These are accepted as a necessary limitation of the general value of the test. The fact that the test does not give positive results in all patients with angina pectoris decreases the value of the test, but does not completely invalidate it. Unfortunately, when such tests were first described, before this limiting factor was appreciated, negative results had been accepted as proving the absence of heart disease. In at least 1 case where anoxia was used to induce electrocardiographic changes,[19] the lack of change was made the basis for recommending discontinuance of insurance disability benefits.

False Positive Tests. Because of their clinical and emotional implications, false positive tests seriously limit the value of the test. While they have not been reported frequently, "Unfortunately, in a very emotionally unstable person, electrocardiographic abnormalities may appear even in such an objective examination as the '2-step' exercise electrocardiogram or the 10 per cent oxygen test."[20] The recommendation that ergotamine derivatives be used to differentiate between the positive results seen in psychoneurosis from those observed in patients with coronary artery disease[20] indicates that false positive tests occur in this important situation, where an accurate test is so urgently needed. As stated above, control studies in a series of normal adults over 50 years of age are in order.

Safety. If the test is not performed in patients with known coronary artery disease, such as those with previous myocardial infarction or those whose resting electrocardiograms are abnormal, it is undoubtedly as safe as any procedure carried out in patients with angina pectoris. However, if the test is limited to those cases where the diagnosis is in doubt, it will be of little value. A test that gives negative results in a high percentage of patients with undoubted angina pectoris and gives positive results in an unknown percentage of subjects without coronary artery disease cannot be relied on in the borderline cases where it is most needed.

Summary

The diagnosis and differential diagnosis of angina pectoris depend on obtaining an adequate history. Problems in diagnosis arise because of confusion of terminology, language difficulties, symptoms resembling noncardiac disease or vice versa, and the coexistence of angina pectoris with disease of other organs. Problems in differential diagnosis arise because symptoms resembling angina may result from disease or abnormal function of the brain, skeletal system, gastrointestinal system, or structures in the bony thorax or within the thoracic cage. The most difficult problems in differential diagnosis arise from psychoneurosis and gallbladder disease. Careful history taking will resolve the problem in most instances, prolonged observation will settle the question in others. To date, no objective tests have been adequate to determine whether or not the patient is subject to attacks of pain due to the physiologic effects of coronary artery pathology or dysfunction.

Summario in Interlingua

Le diagnose e le diagnose differential de angina de pectore depende del obtention de un

historia adequate. Problemas diagnostic se subleva a causa de confusion terminologic, difficultates linguistic, similitude de symptomas in angina de pectore e morbo non-cardiac, e le coexistentia de angina de pectore con morbos de altere organos. Problemas del diagnose differential se subleva proque symptomas de apparentia associabile con angina pote resultar de dysfunction o de morbo del cerebro, del systema skeletal, del systema gastrointestinal, e de structuras in le thorace ossee e intra le cavia thoracic. Le plus difficile problemas del diagnose differential resulta ab psychoneurosis e morbo del vesica biliari. Grande attention prestate al historia del patiente individual va resolver le problema in le majoritate del casos; observationes prolongate va resolver lo in alteres. Al tempore presente il non ha un test objective que es demonstratemente adequate pro determinar si o non le patiente suffre de attaccos de dolor que resulta del effectos physiologic de pathologia del arteria coronari o de dysfunction.

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Proposals for Ballistocardiographic Nomenclature and Conventions: Revised and Extended

Report of Committee on Ballistocardiographic Terminology

By William R. Scarborough, M.D., and Samuel A. Talbot, Ph.D.

The committee's first report, published in *Circulation* for June 1953, recommended a terminology and certain conventions for recording ballistocardiograms of the type then in use. However, it soon became apparent that the committee's work was far from complete.

Increasing knowledge of ballistic theory soon began to throw light on the relations of records secured by various instruments to one another, and a rapid advance in instrumentation began to provide records related to, but often not identical with, those which had been provided with a standard terminology by the committee in its first report. Accordingly, the committee has continued its labors to provide the rapidly advancing field with a uniform terminology.

While they were thus engaged, attention was called to the fact that the designation of spatial axes previously recommended for vector ballistocardiograms differed from that which had been recommended for electrocardiograms by another committee of the American Heart Association. The advantages of a common system for designating spatial axes were obvious to all. Accordingly, as the electrocardiographic usage had priority and as little had been published in the field of ballistocardiographic vectors the committee voted to withdraw their original recommendation and substitute one conforming to that in use by electrocardiographers. In the present communication this new convention is also set forth.

All members of the committee have shared in the deliberations and taken part in the decisions which form the basis of this report; but so much of the larger proportion of the actual work fell on Dr. Scarborough and Dr. Talbot that it was agreed without dissenting vote that only their names should appear as authors. This report has the endorsement of the committee as a whole, and the terminology it suggests is recommended as the official terminology of the American Heart Association.

John R. Braunstein — Maurice B. Rappaport
William Dock — William R. Scarborough
W. F. Hamilton — John E. Smith
John L. Nickerson — Samuel A. Talbot
Isaac Starr, *Chairman*

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2. Nomenclature for Ballistocardiograms.
3. Calibration.
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2. Nomenclature for Ballistocardiograms.
3. Calibration.
4. Suggestions Concerning Technical Data to be Included in Publications.
C. Ultra-low Frequency or Aperiodic Ballisto-

* From the Department of Medicine, Johns Hopkins Medical School and Hospital, Baltimore, Maryland, and from the Howard Hughes Medical Institute.

This is a report of the Committee on Ballistocardiographic Terminology created by the American Heart Association and reflects that Committee's findings in the matter under study.

cardiographic Systems (Gordon; Henderson; von Wittern; Talbot; Burger; Rappaport): UF-BCG.
1. General Characteristics.
2. Nomenclature for Ballistocardiograms (Displacement, Velocity, and Acceleration.)
3. Calibration.
4. Suggestions Concerning Technical Data to be Included in Publications.

D. Direct Body Ballistocardiographic Systems (Dock; Smith; Arbeit; Walker): DB-BCG.
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This appendix has not been included in the present article, but it has been reproduced by the American Heart Association and copies may be secured by writing to Dr. William R. Scarborough, Department of Medicine (Physiological Division), The Johns Hopkins Hospital, Baltimore 5, Maryland, or to the Medical Director of the American Heart Association.

I. Introduction

THE Committee on Ballistocardiographic Nomenclature was originally appointed to study the question of terminology and conventions used in ballistocardiography and to make recommendations aimed at greater uniformity and consistency in the usage of terms in publications on this subject. The rapid growth of the field and the introduction of a variety of new and different ballistocardiographic methods began to produce such confusing differences in terminology and frames of reference that it seemed desirable to attempt to formulate a body of general terms and definitions relating to ballistocardiography. The Committee's brief first report,[1] published in June 1953, dealt with certain conventions to be used in recording and reproducing ballistocardiograms and included recommendations for a terminology for the standard displacement records from the ballistocardiographic instruments in use at that time. The development of newer instruments and technics yielding different types of ballistocardiograms, required that the original recommendations be revised and extended. The current proposals are more comprehensive and detailed than those in the First Report and are intended to supplant them.

This report was designed to provide a practical and meaningful system of terminology, broad enough to apply to the various types of records from all of the different ballistocardiographic instruments now in use. The proposals therefore apply not only to the displacement records from *high frequency* (Starr) and *low frequency* (Nickerson) beds but also to the displacement, velocity, and acceleration records from the *direct body* (Dock) and *ultra-low frequency* ballistocardiographic systems.* The 4 general types of ballistocardiographic systems are treated separately, inasmuch as records of the same aspect of motion (displacement, for example) from different ballistocardiographic systems may be quite different in pattern (fig. 4) and physical content. In each case there is a brief outline of the physical characteristics of the method, a description of the recommended terminology and suggestions regarding the kind of technical

* This Technical Appendix has been prepared by Drs. Scarborough and Talbot in order to provide those interested in the field with important information related to the general theory and design of ballistocardiographs and to the characteristics of electric equipment available for their construction. Its table of contents is given above.

* For economy of space, the names of the four systems may be abbreviated as follows: "HF-BCG" for "high frequency (Starr) ballistocardiograph"; "LF-BCG" for "low frequency (Nickerson) ballistocardiograph"; "DB-BCG" for "direct body (Dock) ballistocardiograph"; "UF-BCG" for "ultra-low frequency ballistocardiograph."

data which should be included in publications. Ballistocardiographic methodology is an exceedingly complex and, at present, poorly understood field. For this reason the authors made no attempt to describe the mechanical performance of the various methods in use[16-19] nor did they attempt to standardize technics for recording ballistocardiograms.

In proposing the nomenclature contained herein every effort was made to base the terminology and conventions on sound physical principles without, insofar as possible, interfering with customs already established. Although the several types of ballistocardiographic systems were treated separately, the same parent nomenclature was used for all systems. The most widely used terminology, that devised by Starr[9] (the ballistocardiographic waves being given the capital letters G through O), forms the basis of wave identification in the records from all the different types of instruments.

Recent biophysical studies[5-8] have revived interest in ballistocardiographic instruments similar in principle to those originally described by Gordon[3] in 1877 and by Henderson[4] in 1905. These instruments which either have an extremely low natural frequency or no natural frequency (aperiodic) are referred to as "ultra-low frequency ballistocardiographs," a term coined by Rappaport.[8] The application of these instruments has thus far been so limited that no record terminology has been fixed by use. The *acceleration* records from these systems are sufficiently similar in appearance and physical content to the standard Starr high frequency ballistocardiograms (fig. 5) that it seemed reasonable, as Deuchar[15] suggested, to extend the older terminology to these new records as well. A different notation has been described in an excellent monogram in Dutch by Elsbach,[10] who was associated with Burger and Snellen; their terminology was given very careful study before a decision was made to recommend the notation contained in these proposals.

The Terminology Committee considered the advisability of assigning names to the waves of ballistocardiograms abnormal in form but concluded that the present practice of using suitable descriptive terms is the simplest and most useful one. Consequently, a terminology is given only for normal records or those in which waves can be identified with reasonable certainty.

The Committee also agreed that there is not yet sufficient information relating to types of ballistocardiograms other than the usual longitudinal (head-foot) record to justify a nomenclature for them. In the interest of uniformity of recording and presentation, however, standard spatial axes and conventions of polarity were recommended. (These are somewhat different from those described in the First Report.)

During the preparation of this report, the authors realized that certain technical information might be useful to those in the field in clarifying some of the problems of ballistocardiographic methodology. Inasmuch as this information had no place in the Terminology Proposals, a Technical Appendix was prepared; its composition is shown in the foregoing outline. The length of the Appendix and its technical nature made it unsuitable for publication along with the Proposals. However, it has been printed and may be obtained from the authors on request.

The terminology and conventions proposed in this report should, in no sense, be considered final and irrevocable. Further advances in our understanding of ballistocardiographic methods and the information they supply will almost certainly require modifications and additions in the future.

II. Conventions Applying to all Ballistocardiographic Systems

A. *Standard Spatial Axes and Conventions of Polarity (figs. 1 and 2).*

1. For Ballistocardiographs Recording Translations:
   a. Transverse (side to side) axis (x): rightward positive, leftward negative.
   b. Longitudinal (head-foot) axis (y): headward or cephalad positive, footward or caudad negative.
   c. Dorsoventral (anteroposterior) axis (z): dorsal positive, ventral negative.
2. For Ballistocardiographs Recording Rotations:

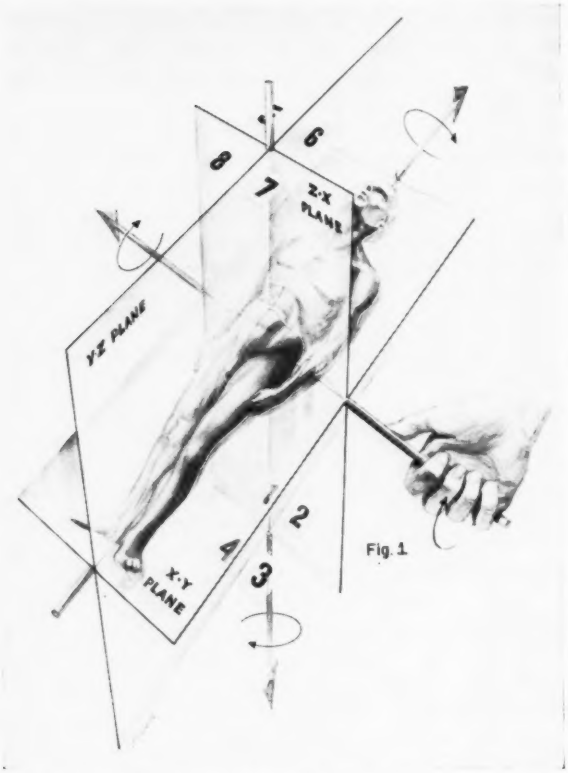

Fig. 1

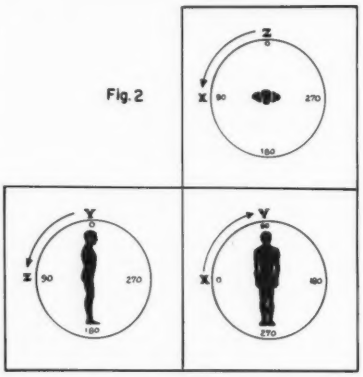

Fig. 2

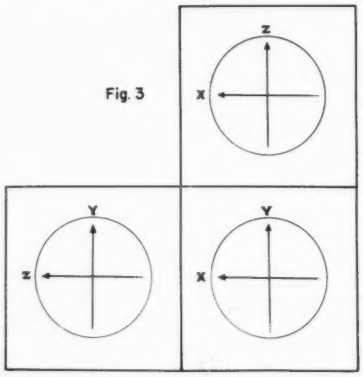

Fig. 3

FIG. 1. Ballistocardiographic spatial axes and conventions for polarity. In the 3 axes the arrows point in the positive direction. (See text.)

FIG. 2. The body in 2- and 3-dimensional projections to illustrate reference planes.

FIG. 3. Conventions for presentation or reproduction of vector ballistocardiographic records. The conventions for the frontal, sagittal, and transverse planes are shown. (See text.) (These figures are reproduced through the courtesy of Dr. John R. Braunstein who prepared them.)

a. About the transverse axis (x): Clockwise (viewed from the subject's left side) positive, counterclockwise negative.
b. About the longitudinal axis (y): Clockwise (viewed from the subject's feet) positive, counterclockwise negative.
c. About the dorsoventral axis (z): Clockwise (viewed from the subject's front) positive, counterclockwise negative.

B. *Conventions for Presentation or Reproduction of Ballistocardiograms.*

1. Scalar Ballistocardiographic Records:
   a. In all scalar records time should move from left to right.
   b. Positive polarity should be inscribed or reproduced upward; negative polarity downward.
   c. Some event in the cardiac cycle (electrocardiogram, pulse, or heart sounds) should be recorded simultaneously to permit identification and timing of waves.
2. Vector Ballistocardiographic Records: (fig. 3)

   It may be noted that in each plane positive deflections will be upward and to the observer's left as he stands before the scope face.

   a. Frontal plane (x, y):
      Longitudinal axis (y) is displayed vertically with positive polarity upward.

Transverse axis (x) is displayed horizontally with positive polarity to observer's left.

b. Sagittal plane (y, z):
Longitudinal axis (y) is displayed vertically with positive polarity upward.
Dorsoventral axis (z) is displayed horizontally with positive polarity to observer's left.

c. Transverse plane (x, z):
Dorsoventral axis (z) is displayed vertically with positive polarity upward.
Transverse axis (x) is displayed horizontally with positive polarity to observer's left.

C. *General Definitions and Terminology.*

1. The Baseline:

For most kinds of ballistocardiograms the baseline may be defined as the "neutral" line of the record indicating the position of the body when it is motionless. A reasonably flat baseline is often seen in late diastole when the body's oscillations are minimal or have ceased. If a flat baseline is not visible it may be approximated by placing a horizontal line midway between the opposing tips of the small waves in late diastole. In records secured by electric amplification the baseline can be obtained by rapidly reducing the sensitivity until amplitudes become negligible, provided this has no effect on centering.

In *displacement records from ultra-low frequency ballistocardiographs*, the selection of a baseline is an arbitrary matter. There is usually no flat baseline because at normal pulse rates the motion of the body and support never ceases, one cardiac cycle merging into the next. In practice, an arbitrary horizontal baseline may be placed by drawing a straight line through the displacement GH segment (GH) in successive beats. In velocity and acceleration records from the ultra-low frequency systems flat baselines may be present in diastole. If not, they may be placed in the same manner as that employed for the displacement records, using the GH segment in each case. (See also Technical Appendix, Section F.)

2. Parts of Waves:

The point of a wave, directed upward or downward, may be called the *tip*, for example, "the K wave tip."

The part of the record joining the tip of one wave with the tip of the next wave is to be called a segment, for example, "the IJ segment."

III. Recommendations Regarding Normal Records from Different Types of Ballistocardiographic Systems:—Longitudinal (head-foot) Ballistocardiograms

A. *High Frequency Ballistocardiographs (Starr-type[9]): HF-BCG.*

1. General Characteristics:

a. A table, "bed," or platform provides support for the body. A footboard is generally used to improve the coupling between the two.

b. Stiffness of springs coupling platform to ground is 10–100 times greater than the stiffness of the body's dorsal springs.* (1,000–30,000 lbs./in. compared with 200–300 lbs./in.)

c. No external damping (except that introduced by the body).†

d. Platform weights range from 20 to 100 lbs. (from 1 to $\frac{1}{10}$ of adult body weights).

e. Loaded with 150 lbs. dead weight, platform natural frequencies range from 8–14 c/s, depending on the stiffness of the platform spring.‡

f. Loaded with a human subject the fundamental frequency of bed-body combination ranges from 3–9 c/s, depending on coupling between patient

* The *stiffness* or *spring constant*, k, of a flexible member represents the *force* required to produce a unit deflection.

† *Damping* is the progressive reduction in amplitude of vibration of an elastic body due to viscous frictional forces tending to oppose its motion.

‡ *Natural frequency* is the rate, in cycles per second, at which a (lightly damped) elastic body vibrates back and forth when it is set into motion and allowed to oscillate freely.

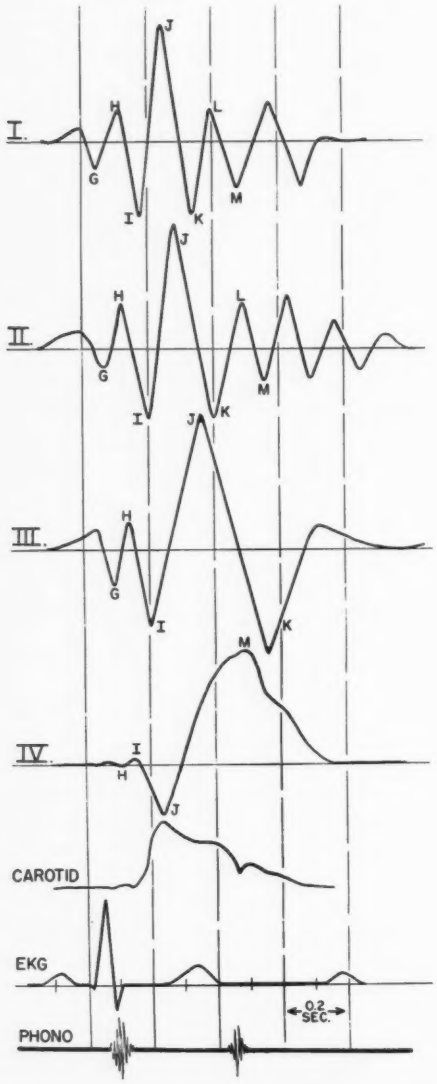

FIG. 4. Reproduction of *displacement* records from different ballistocardiographic systems to show differences in timing of waves and relationship between waves and the carotid pulse, electrocardiogram, and phonocardiogram. Vertical lines are 0.2 sec. apart. Initial solid line marks the Q wave of the electrocardiogram. I. High frequency ballistocardiogram. II. Direct body ballistocardiogram. III. Low frequency ballistocardiogram. IV. Ultra-low frequency ballistocardiogram.

and platform; usually it averages about 5 c/s.

2. Nomenclature for Ballistocardiograms:
   a. Normal displacement records (fig. 4).
      (1) Recommended nomenclature:
         (a) Systolic waves.
            (i) The H wave is a headward deflection which begins its ascent at or near the peak of the electrocardiographic R wave. Its peak is at or near the beginning of ejection.
            (ii) The I wave is the footward deflection following the H wave in normal records; it occurs early in systole.
            (iii) The J wave is the largest headward wave in the normal record; it immediately follows the I wave, and occurs late in systole.
            (iv) The K wave is the footward wave following J; it occurs near the end of systole.
         (b) Diastolic waves.

The two smaller headward waves which usually follow the K wave in normal records are to be called L and N, the footward wave between them is to be called M. The small waves, occurring later in some normal records may be given the letters in sequence.

However, the large diastolic waves occurring in certain abnormal records are not to be given these letters as they are believed to be due to forces quite different from those which produce the smaller normal waves. Those abnormal waves should not be given a letter, but should be

described by their direction and position, for example, "A large headward wave occurring in late diastole."

(c) Presystolic waves.

The G wave is the small footward wave which at times precedes the H wave.

A headward wave preceding G, not described by most authors, should be called F, if it is encountered, but any wave thus lettered should be clearly derived from presystolic forces such as atrial contraction and not be an after-vibration from forces liberated in the preceding systole.

These ballistocardiograms, unlike other types of displacement records, show no weaving or undulation of the baseline with respiration.

b. Velocity records: No recommendations.

c. Acceleration records: No recommendations.

3. Calibration; High Frequency Ballistocardiographs (HF-BCG):

a. Displacement calibration:

The ordinate of the displacement HF-BCG should be calibrated by adjusting the amplification so that a standard platform displacement produces a standard deflection of the baseline, e.g. 2×10^{-4} cm. platform displacement/cm. deflection on record. The standard deflection is obtained by applying a corresponding deflection force (pulley and weight) to the platform (see Technical Appendix); this force should be stated.

b. Force calibration:

The classical method of calibration is to set the amplification to produce 1 cm. deflection in record/280 Gm. force applied to platform. Displacement calibration is preferred for reasons stated in the Technical Appendix.

c. Dynamic calibration: See Technical Appendix.

4. Suggestions Concerning Technical Data to be Included in Publications.

In order to compare records from different instruments of this type, it is recommended that certain physical constants be measured (if possible) and set forth in publications. These include:

a. Calibration (see above).

b. Weight of platform.

c. Spring constant, k, of platform; *or* weight and natural frequency of platform alone. ($k = f^2 \times 0.1$ wt., where weight is in lbs., k in lbs./inch and f in cycles/sec.)

d. Characteristics of transducer, recorder, and associated electric equipment.

Other important data are: natural frequency, damping and weight of the platform—body combination. (See Technical Appendix.)

B. *Low Frequency Ballistocardiographs (Nickerson-type[11]): LF-BCG.*

1. General Characteristics:

a. A table, "bed," or platform provides support for the body and a footboard is generally used to improve the body's coupling.

b. Springs coupling platform to ground are about $\frac{1}{5}$ as stiff as the body springs.

c. Platform weights are usually about the same as those with the high frequency beds.

d. Platform is critically damped with dead weight on platform equaling weight of subject.

e. Loaded with dead weight (equal to patient's weight) platform frequency is set at about 1.5 c/s.

2. Nomenclature for Records:

a. Normal displacement records (fig. 4).

(1) Recommended nomenclature:

The wave form in these records

somewhat resembles that observed in high frequency ballistocardiograms. The waves in these records should be designated by the same letters (G, H, I, J, and K) as those in high frequency ballistocardiograms. They are in the same direction but considerably later in time. The J wave usually occurs in late systole, or early diastole and the K wave in mid-diastole. There are normally no other recognizable diastolic waves.

Respiration causes rather large fluctuations of baseline in these records but this is abolished when respiration is suspended.

b. Velocity records: No recommendations.

c. Acceleration records: No recommendations.

3. Calibration of Low Frequency Ballistocardiographs (LF-BCG):

a. Displacement calibration:

The scale of the ordinate should be adjusted, measured, and expressed in the same way as for the high frequency bed, e.g. .005 cm. platform displacement/cm. deflection on record.

b. Force calibration:

The classical calibration is to adjust the gain so that a known force (usually 35 or 40 Gm.) applied to the platform by means of a weight, produces a 1 cm. deflection on record. This is expressed: 40 Gm. force/cm. deflection on record. Calibration (a) is preferred because of dynamic disproportion between force and displacement, as in the case of the HF-BCG.

4. Suggestions Concerning Technical Data to be Included in Publications:

Same as for high frequency ballistocardiograph.

C. *Ultra-low Frequency or Aperiodic Ballistocardiographs (Gordon[3]; Henderson[4]; von Wittern[5]; Talbot[6]; Burger[7]; Rappaport[8]): UF-BCG.*

1. General Characteristics:

a. A platform or hammock, which is relatively stiff horizontally, supports the body. Additional coupling of body to platform is obtained with a footboard or other constraints.

b. Stiffness of spring coupling platform to ground is only 0.01–0.002 of the stiffness of the body's dorsal spring.

c. A small amount of external damping is generally used.

d. Weights of the supporting surface range from 3–20 pounds (1/6 to 1/60 of body weight). This is suspended so as to minimize vertical or flexural vibrations.

e. Platform frequencies (unloaded or loaded with dead weight) range from 0 to about 0.5 c/s.

f. Loaded with human subject the fundamental frequency of bed-body combination ranges from 0–0.5 c/s.

2. Nomenclature for Records:

a. Normal acceleration records. (See figs. 5 and 6)

The normal ballistocardiograms of this type generally resemble the normal displacement records from high frequency and direct body ballistocardiographs. They differ from the latter types in that: (1) They have a less sinusoidal appearance; (2) the K wave is usually small or absent; (3) there may be extra waves or deflections; (4) corresponding wave tips are slightly early in time; and (5) they tend to show faster detail. Under ordinary circumstances respiration causes no baseline weave.

In these records the waves which are similar in direction and time to the G, H, I, J, L, M, and N waves in high frequency bed and direct body displacement ballistocardiograms should be designated by the same letters.

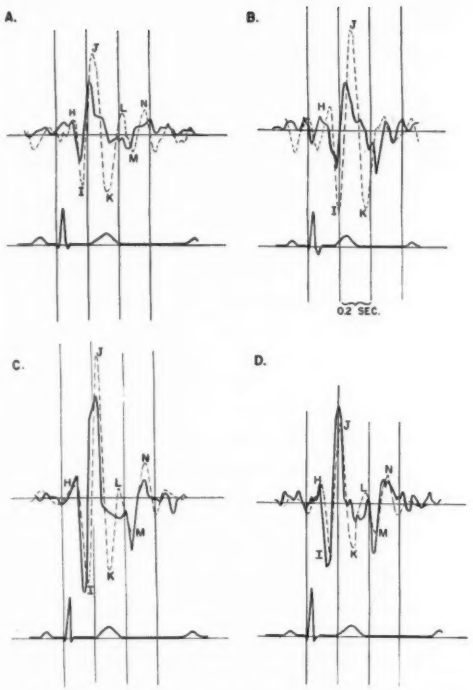

FIG. 5. Comparison of displacement ballistocardiograms (broken lines) from a high frequency system with acceleration ballistocardiograms (solid lines) from an ultra-low frequency system (mercury bed). Single complexes from the normal records of 4 subjects studied with each instrument are traced and superimposed to demonstrate the relationship in time and wave form. The electrocardiogram provides a reference for timing in each case. Vertical lines are 0.2 sec. apart. The letters apply to the waves of the high frequency ballistocardiogram. (This figure is reproduced with the permission of *Circulation*.)

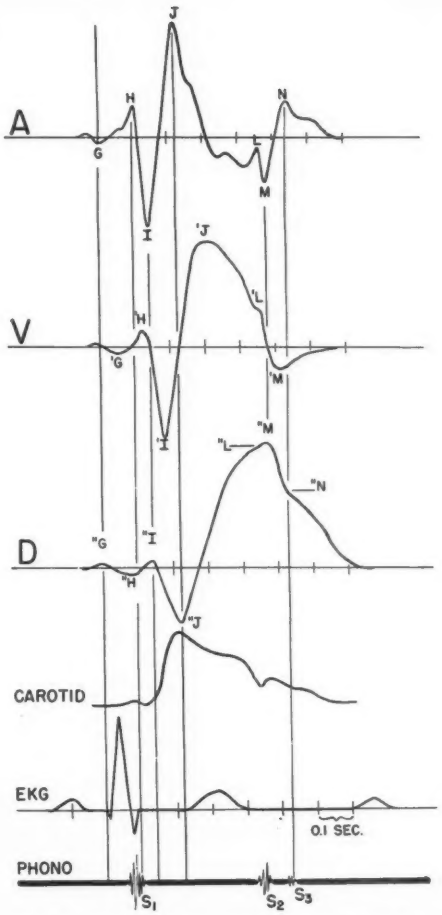

FIG. 6. Normal displacement *D*, velocity *V*, and acceleration *A* ballistocardiograms from an ultra-low frequency system (mercury bed) to show their relationship to each other and to the carotid pulse, phonocardiogram, and electrocardiogram. The tips of the G and ″G, H and ″H, I and ″I, J and ″J, M and ″M waves coincide in time; at each of these points velocity is zero (baseline crossing).

Therefore, H, J, L, and N are positive (headward) waves and G, I, and M are negative (footward) waves.

The details of wave form observed in normal records of this type are greater than that in high frequency records. Not infrequently there are slurs on the HI segment and on the IJ segment. There is considerable individual variation in pattern between the J and M wave tips. (See fig. 5 for differences in detail). There is usually a small headward wave which roughly corresponds to the high-frequency L wave; this should be termed the L wave. Other deflections commonly occurring between J and L may be designated in any manner that seems suitable. This variable portion of the record may be termed "the JL segment" or "the K region."

The H, I, and J waves are in

systole, while the M and N waves are in early diastole; the L wave usually occurs at the time of the second heart sound. Small deflections later in diastole are sometimes present; no specific names are recommended for them.

b. Normal displacement records (fig. 6).

The normal ballistocardiogram of this type bears little resemblance to any other type of ballistocardiographic record although its nearest relative is the low frequency displacement ballistocardiogram (fig. 4). These records are characterized by simplicity of wave-form and absence of detail. There are only 2 major waves, a footward one with its tip in mid-systole and a larger headward wave with its tip in early diastole. After this there is a slight footward flexure, followed by a gradual, sometimes undulating, return.

Respiration causes weaving of the baseline* many times the amplitude of the ballistocardiographic complexes even when the instrument is highly damped. The baseline usually stabilizes if respiration is suspended and the patient lies motionless.

There is a corresponding wave or flexure in these records for each wave tip in the acceleration record; although opposite in direction to the latter they are to be designated by the same letters, G, H, I, J, L, M, and N. A double prime symbol placed before these letters† may be used to distinguish displacement waves (or flexures) from acceleration or velocity waves under any circumstances wherein a distinguishing symbol is needed to avoid confusion. ″H, ″J, ″L, and ″N are footward waves or flexures (concave upward) and ″G, ″I, and ″M are headward waves or flexures (convex upward).

The headward ″G wave if present is small. The footward ″H wave is also small and is often represented only by a bend or flexure before the headward ″I wave tip. The ″I wave is clear-cut but small and is followed by the deep footward ″J, the tip of which is the lowest point of the record. The headward ″M wave is the tallest of the waves of the displacement ballistocardiogram. Preceding the summit of the ″M wave a distinct shoulder or slur is usually present; this coincides in time with the beginning and tip of the acceleration L wave and may be termed the ″L flexure.

The tip of the headward ″M wave usually occurs in early *diastole* and is synchronous with the footward acceleration M wave. Between this point and the beginning of the next cycle, there is a variable pattern. In general the early part of the downstroke is moderately steep and the later part shallow. The transition between the two is usually marked by a distinct negative (footward) bend which corresponds in time to the acceleration N wave tip and may be referred to as the ″N flexure. After this there is usually a gradual footward descent.

c. Normal velocity records (fig. 6).

The normal ballistocardiogram of this type differs considerably from other types of ballistocardiograms. There are 3 major waves: the first is a small, rather narrow footward wave; the second is a large, broad headward wave which usually extends to or slightly beyond the end of systole; the third is a smaller, sharper, footward wave with its tip in early diastole.

* Refer to paragraph on baseline.

† Primes placed *before* the letters are meant to denote *integrals*; double primes are used for displacement (double integral of acceleration) and single primes for velocity (single integral of acceleration). This convention is not to be confused with the one used for designating waves in direct-body records for in the latter case the single and double primes are placed *after* the letters to indicate the 1st and 2nd *derivatives* of displacement which are velocity and acceleration, respectively.

Respiratory weave of the baseline again exceeds the amplitude of the (velocity) ballistocardiogram, with a lightly damped platform. It stabilizes when respiration is suspended.

The tips of the waves in these records are later than the wave tips similarly named in displacement and acceleration records. (See Appendix, section on relation of D, V, and A.) There is usually a small footward wave followed by a small headward wave and a larger footward wave in the same direction as the acceleration G, H, and I respectively, but delayed in time. These may be designated by the same letters adding, when needed, a single prime before the letters to indicate they are velocity waves; for example, "the 'I wave." The next succeeding wave, the 'J, is the dominant headward wave. After 'J a well marked rather rapid upward deflection is usually present; this may be termed the 'L wave although it is slightly later in time than the acceleration L wave and the displacement "L flexure. The final major wave 'M, is footward, and its tip follows the acceleration M and displacement "M waves.

The time relationships between displacement, acceleration, and velocity records may be checked by the following rule: The velocity tracing crosses the baseline at the tips of the "H, "I, "J, and "M displacement waves and at the tips of the H, I, J, and M acceleration waves.

3. Calibration of Ultra-low Frequency Ballistocardiographs (UF-BCG):
   a. Acceleration records:
      (1) The record should be calibrated by adjusting the amplification so that a standard acceleration of platform or accelerometer produces a standard deflection of the baseline, for example: 2 cm./sec.^{2}/cm. chart deflection.

      The frequency range over which this calibration applies should be stated. (See Technical Appendix for methods of producing standard accelerations and finding passband.)

      (2) Force sensitivity: The ordinates of the acceleration record should not be scaled in force units, as the relation of BCG force to platform acceleration is unclear.

   b. Velocity records:

      The velocity should be calibrated by amplifier adjustment so that a standard velocity of platform or transducer produces a standard deflection of the baseline, for example: 0.1 cm./sec. platform velocity/cm. chart deflection. The passband over which this applies should also be given, for example: "over the range 1–20 c/s." (Methods of producing standard velocity and measuring the passband are given in the Appendix.)

   c. Displacement records:

      The displacement record should be calibrated by so adjusting the amplifier that a standard displacement of platform or transducer produces a standard chart deflection, for example: 0.05 mm. platform motion/cm. chart deflection over the range 1–20 c/s. (The Technical Appendix gives method of producing standard deflection and measuring passband with the transducers generally used with the UF-BCG.)

4. Suggestions Concerning Technical Data to be Included in Publications:

   In order that records from different instruments of this type may be compared, certain physical characteristics should be described. These include:

   (1) Type of support and nature of its coupling to "ground."
   (2) Construction and weight of platform.
   (3) Natural frequency and damping of platform.
   (4) Methods used to increase coupling of body to platform (footboards, etc.).

(5) Type of transducer and characteristics. (See Technical Appendix.)
(6) Description of any differentiators, integrators, or filters used.
(7) Over-all frequency response characteristics (phase and amplitude) and calibration values for the whole ballistocardiographic system, if known. (See Technical Appendix.)

D. *Direct Body Ballistocardiographs.* (*Dock*[2]; *Smith*[12]; *Arbeit*[13]; *Walker*[14]): *DB-BCG.*

1. General Characteristics:
   a. Body is not supported on a spring-coupled platform. Patient usually reclines on a rigid flat surface but other surfaces are used.
   b. The motion of a single part of the body is recorded. Most commonly a crosspiece connecting the two shins is used; its motion is referred to the supporting surface. The top of the skull and other points on the body have also been used.
   c. Since there is no spring-coupled supporting platform, the mechanical characteristics are those of the human body. Of the 3 variables, body mass, spring constant, and damping, the latter 2 vary (or can be made to vary) depending on: (1) the kind of supporting surface used (hard surface, rubber, sand, putty, etc.), (2) how the body is supported (blocks or sandbags beneath the heels, pillows for the head, etc.), and (3) nature, location, and tightness of added couplings, if any (footboard or hip, shoulder, chest, and head supports).

   For the average patient lying on a hard floor with blocks under the heels, and a small pillow to support the head, reasonable values for spring constant (k), body natural frequency (f_n), and damping (ζ), are k = ±240 lbs./in.; f_n = ±4 c/s; ζ = ±.15 (15 per cent of critical). Changes in these physical factors may cause changes in the dynamic performance of the body-ballistocardiographic system and therefore changes in the ballistocardiographic records. In practice, an attempt is made to keep as invariant as possible the conditions under which routine records are taken. Different operating conditions are currently in use and no standard method is proposed.
   d. The transducer used to sense the motion of the body constitutes a second spring-coupled mass which may or may not modify the recorded ballistocardiogram depending on the transducer's physical characteristics. With the shin crosspiece type of transducer, distortion of the record is reduced by (1) reducing weight of crosspiece, (2) increasing coupling between crosspiece and shins, and (3) reducing or removing coupling between crosspiece and body support.
   e. In general, frequency response characteristics of direct body ballistocardiographic systems (including body) are rather similar to those of the "high frequency" systems. (See Appendix.)
2. Nomenclature for Records:
   a. Normal displacement records (fig. 7).

      Most ballistocardiograms of this type show a rather close resemblance in waveform to the displacement records from the high frequency ballistocardiograph but are somewhat later in time (fig. 4). Unlike the latter, there is respiratory baseline weave which disappears during suspended respiration. Records taken from other parts of the body along the longitudinal axis resemble, in a general way, those from the shins but they may differ in various details.

      The waves in these records, similar in direction and time, should be designated by the same letters given the corresponding waves in the high frequency ballistocardiogram, that is, G, H, I, J, K, L, M, N, and O.
   b. Normal acceleration records (fig. 7).

      Ballistocardiograms of this type

roughly resemble displacement and velocity records, the latter more than the former. In the acceleration record the waves are sharper, there is more rapid detail (notching, slurring, etc.) and greater susceptibility to ambient vibration. Respiration does not cause baseline weave.

The waves of the normal acceleration ballistocardiogram are to be given the same letters as those waves in the displacement record which are synchronous in time but opposite in direction. The double prime symbol placed after the letters* denotes acceleration waves. H″, J″, and L″ are negative or downward and their tips coincide with those of the positive H, J, and L waves in the displacement record. Similarly, G″, I″, K″, and M″ are positive or upward and their tips coincide with those of the negative G, I, K, and M waves.

c. Normal velocity records (fig. 7).

Ballistocardiograms of this type bear a general resemblance to the related displacement ballistocardiograms. They differ in that there is usually no baseline weave with respiration, they contain faster detail, and the waves are earlier in time.

The waves of the normal velocity ballistocardiogram are to be assigned the same letters as those given to waves of similar appearance and polarity in displacement records although the velocity waves appear earlier in time. The velocity waves are to be distinguished by the single prime symbol placed after the letters. H′, J′, and L′ are positive (headward) waves and I′, K′, and M′ are negative (footward) waves.

Although tips of normal displacement and acceleration waves occur synchronously, this is not true for velocity waves. However, the correct time relationship of the normal velocity record with the other two can be checked by means of the following rule: Velocity is always zero (baseline crossing) at the tips of displacement and acceleration waves. Thus, each intersection of the velocity tracing with the baseline serves to

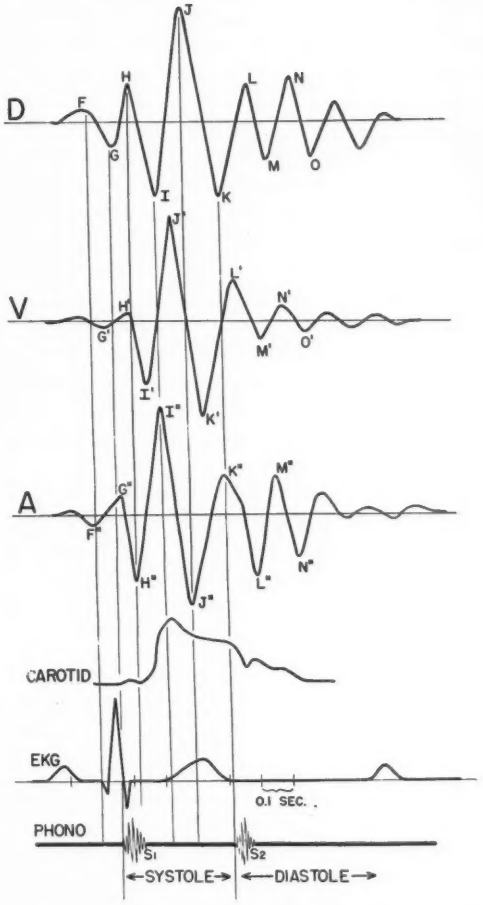

FIG. 7. Normal displacement D, velocity V, and acceleration A ballistocardiogram from a direct body system to show their relationship to each other and to the carotid pulse, electrocardiogram, and phonocardiogram. The tips of the G and G″, H and H″, I and I″, J and J″, M and M″ waves coincide in time; at each of these points velocity is zero (baseline crossing).

* Single and double primes *after* the letters are used to indicate the first and second derivatives of displacement which are velocity and acceleration, respectively.

mark the temporal positions of the displacement and acceleration wave tips.

3. Calibration of Direct Body Ballistocardiographs (DB-BCG):
   a. Displacement calibration:

      The record should be calibrated by so adjusting the amplification that a standard displacement of the shin (or head) piece produces a standard chart deflection, for example; 0.006 cm. displacement of shin piece/cm. chart deflection, over the range 1–20 c/s. Appendix gives method of determining these with usual DB-BCG transducers, and the correction for resonant motion of the shin piece.

   b. Velocity calibration:

      Similarly, the gain adjustment should be described, for example: 0.1 cm. per sec. velocity of shin piece/cm. chart deflection, over the range 1–20 c/s. (See Technical Appendix for methods.)

   c. Acceleration calibration:

      The acceleration record should be scaled by similar adjustment, for example: 2 cm./sec.^{2} acceleration of shin piece/cm. chart deflection, over the range 1–30 c/s. (See Technical Appendix for methods.) *Note:* Some commercial assemblies preadjust the ratios of gain for the 3 aspects of motion, so that stated calibrations of motion result for a prescribed sensitivity of the amplifier, for example: 1 mv./cm. deflection of record. In this case also the range should be stated over which the calibration applies.

4. Suggestions Concerning Technical Data to be Included in Publications:

   In order that records from different instruments of this type may be compared, the method used should be described as clearly and completely as possible. This description should include the following items:

   a. Method of supporting body: type of supporting surface, (hard, rigid surface; sand, putty, etc.), shin blocks, pillows, padding, constraints, etc.
   b. Transducer, recorder, and associated electric equipment. The type of instrument (electromagnetic, photoelectric, piezoelectric, etc.) used should be indicated. If filters, integrators, differentiators, and other electric devices are used this should be stated. They need not be described if the complete over-all performance data are given. (See Technical Appendix.) For example, the following statement would provide sufficient description of the performance of the instrument. "Displacement, velocity, and acceleration records were obtained using an electromagnetic pickup in association with an integrator, a differentiator, and high cut filters. In all 3 cases over-all performance indicated that there was less than 15° phase shift and less than 15 per cent amplitude error from 1–20 c/s."

      If performance data are unknown, then the actual values (resistance, capacitance, etc.) of all the electric components should be given and, if it seems warranted, a circuit diagram should be shown. Appropriate calibration values also should be given.
   c. Coupling of transducer to body:

      If part of the transducer is applied to be body, its weight, the way in which it is coupled to the body and, if possible, the natural frequency of this coupling should be indicated. Also, if the body is coupled through the transducer to the supporting surface, the nature of this coupling (stiffness, natural frequency, etc.) should be indicated. (See Technical Appendix for method of testing.) With most electromagnetic and photoelectric transducers there is no physical connection between the part of the transducer on the body and the part on the table; with other types there is usually some coupling between the 2 parts.

IV. Summary

1. Revised and extended proposals for ballistocardiographic nomenclature and conventions are presented.
2. Proposed conventions applying to all ballistocardiographic systems include:
   a. Standard spatial axes and conventions of polarity.
   b. Conventions for presentation or reproduction of ballistocardiograms.
   c. General definitions and terminology.
3. Current ballistocardiographic instruments are classified in 4 separate types and treated individually. For each type the general characteristics of the method are given along with suggestions regarding calibration and other technical data to be included in publications.
4. A terminology for waves, based on Starr's original system, has been devised for displacement records from the high frequency (Starr) and the low frequency (Nickerson) ballistocardiographs and for displacement, velocity, and acceleration records for direct body and ultra-low frequency ballistocardiographs.
5. These new proposals are endorsed by the Committee on Ballistocardiographic Terminology and are intended to supplant the earlier proposals set forth by this Committee.

Summario in Interlingua

1. Es presentate revidite e augmentate proponimentos pro le nomenclatura e le conventiones ballistocardiographic.

2. Le proponimentos de conventiones applicable a omne systemas ballistocardiographic representa le sequente categorias:

a. Standard axes spatial e conventiones de polaritate.

b. Conventiones in le presentation e reproduction de ballistocardiogrammas.

c. Definitiones e terminologia general.

3. Le instrumentos ballistocardiographic que es currentemente in uso es dividite in quatro typos separate. Iste typos es tractate individualmente. Pro omne typo le characteristicas general del methodo es presentate insimul con propositiones relative al calibration e altere datos technic que debe esser includite in publicationes.

4. Quanto al undas, un terminologia basate super le systema original de Starr esseva elaborate pro registrationes de displaciamento ab ballistocardiographos a alte frequentia (Starr) e basse frequentia (Nickerson) e pro registrationes de displaciamento, velocitate, e acceleration ab ballistocardiographos directe e ab balistocardiographos a ultrabasse frequentia.

5. Iste nove proponimentos ha le approbation del Committee pro le Terminologia Ballistocardiographic. Le intention del Committee es que illos supplanta le proponimentos previemente formulate per illo.

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ABSTRACTS

Editor: SAMUEL BELLET, M.D.

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ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY and BALLISTOCARDIOGRAPHY

Jouve, A., Corriol, J., Albouy, M., Velasque, P., and Avril, P.: The Cardiac Electric Field of the Dog after Injection of Caustic Substances into the Myocardium and Its Modification by Partial Insulation of the Heart. Arch. mal. coeur **48:** 925, 1955.

In 21 dogs the ventricles were insulated by means of a rubber bag and the effects on the electrocardiogram in the frontal plane and in 3 levels of circumferential unipolar thoracic leads were studied before and after local injection into the ventricle of a viscous paste containing 80 per cent formaldehyde. Insulation of the intact heart caused a constant diminution of the voltage of QRS and T, with only insignificant changes of the configuration of these waves. This observation supports the conclusion that the electric field produced by the intact heart is analogous to that produced by a polarized plane situated at the ventricular orifice. Insulation of the heart after focal lesion always caused diminution and sometimes even complete disappearance of the changes of QRS and S-T caused by the injury. This was the case in all thoracic leads as far as changes of S-T were concerned, but the QRS changes disappeared only in the low-level leads, and remained almost without modification in the high-level leads situated near the opening of the insulating bag.

LEPESCHKIN

Giraud, G., Latour, H., and Puech, P.: Study of the Atrial Activation by Means of Esophageal and Intracardiac Leads in Human Atrial Flutter. Arch. mal. coeur **48:** 817, 1955.

Multiple unipolar and differential esophageal and intracardiac leads were registered synchronously with limb and precordial leads in 11 cases. In 6 cases of flutter of the "common type" the F waves had highest voltage in leads II and III, in which they were usually diphasic (− +) or inverted, while in V_1 they were diphasic (− +) or had an isoelectric initial component. In this type, intrinsicoid deflections appeared only during the first 0.12 to 0.14 sec. of the 0.18 to 0.20 sec. atrial cycle; the rest of the cycle was taken up by the atrial T wave, which had a direction opposite to that of the rapid initial portion of the waves. From the timing of the intrinsicoid deflections it was concluded that in this type of flutter the excitation wave ascends along the posterior wall of both atria and the interatrial septum and descends along the anterior wall of the right atrium. In 2 additional cases the same type of flutter could be provoked during cardiac catheterization by pressure of the catheter against the lower wall of the right atrium, near the coronary sinus or the atrial septum. In a third additional case this type of flutter developed during quinidine treatment of atrial fibrillation, but in this case the atrial cycle and the duration of atrial activation were prolonged to 0.32 sec. and 0.20 sec. respectively. In 1 case of mitral stenosis the F waves were best visible in leads I and aV_L ("rare form of flutter"); the portion of the waves that corresponded to atrial activation was upright in lead I and diphasic (+ −) in V_1. In this case atrial activation proceeded downward on the anterior as well as the posterior wall of the right atrium. These findings are not consistent with the circus-movement theory of flutter, but rather with a single focus of rapid stimulus formation, accompanied by a variable degree of intraatrial conduction delay.

LEPESCHKIN

Real, A. P.: Organic-Functional Left Bundle Branch Block. Rev. espanol. de cardiol. **9:** 301 (Aug.), 1955.

In a 44-year-old woman with moderate hypertension and angina, left bundle-branch block disappeared after it had been present for 2 years. It is impossible to determine in a given case to what extent block is due to organic interruption and to what extent it is due to a functional conduction delay in the remaining few fibers of the bundle.

LEPESCHKIN

Borter, P., and Muller, P.: The Electrophonocardiogram in Exercise. Cardiologia **27:** 194 (Fasc. 4/5), 1955.

Standardized exercise produced in 75 persons the following acute alterations in the apical phonocardiogram: the distance between the Q wave of the electrocardiogram and the second heart sound shortened, and this more than the Q-T interval. The amplitude of the first sound invariably increased; that of the second sound only occasionally. The contour and duration of the sound complexes showed no significant modifications. All these alterations returned to resting values within 5 min. There were no significant differences in the results of exercise tests in normal persons and in persons with diseased hearts. The authors conclude that changes of the phonocardiogram under exercise, while of theoretic interest, have no value in clinical diagnosis.

PICK

Holzmann, M., and Zurukzoglu, W.: The Clinical Significance of Negative and Diphasic U Waves in the Human Electrocardiogram. Cardiologia **27:** 202 (Fasc. 4/5), 1955.

Four hundred and fourteen electrocardiograms were analyzed in 200 patients exhibiting diphasic or negative U-waves in 1 or more conventional leads, as to the clinical significance of this alteration. Eight types of abnormal U-waves resulting in part from their superposition on normal or abnormal T waves were described. Clinical correlation revealed their occurrence in 96 per cent in association with cardiovascular disease, in 2 per cent in the presence of functional disorders, and in 2 per cent in the absence of any heart disease. In 37 per cent of the cases the electrocardiograms were otherwise normal or showed only questionable abnormalities. Among the clinical conditions leading to U inversion, hypertension was in first place, followed by valvular lesions, cor pulmonale, and acute or chronic coronary insufficiency. Vectorial analysis permits a classification of inverted U-waves similar to that of ST-T alterations with respect to localization of the lesions present. The genesis of pathologic U-waves is unknown but it would appear that the development of abnormal inverted as well as upright U-waves is in some way related to changes in the metabolism of the myocardium.

PICK

Schmidt, J.: The Significance of the P Waves in Clinical Electrocardiography. Ztschr. Kreislaufforsch. **44:** 837 (Nov.), 1955.

During sinus rhythm 5 characteristic abnormal P wave patterns can be distinguished that can be correlated with certain alterations in atrial activation. (1) The "P inversum" is represented by a negative P wave in lead I and is the unmistakable sign of transposition of the atria. In association with alterations of the ventricular complex it permits the recognition of various anomalies of the position of the heart. (2) The "P sinistro-cardiale" consists of a broad double-peaked deflection. The second peak in the standard leads shows a left axis deviation; is larger in the left precordial leads than the first peak; and in V_1, is broad and inverted. It can be attributed to left atrial strain. (3) The "P dextrocardiale" occurring in right atrial strain appears as a tall narrow and pointed deflection best seen in leads II and III and in parasternal leads. (4) The "P cardiale" shows characteristics of (2) and (3) and is caused by strain upon both atria. (5) The "Vagus P" is a small, frequently notched deflection associated with bradycardia and tall T waves of the ventricular complexes. With increase of the sympathetic tone, on the other hand, the P wave increases in size and becomes similar to a "P dextrocardiale" while the T wave becomes distinctly flatter.

PICK

Sibille, A., Adam, F., and Dutrieux, J. M.: The Spatial Vectorcardiogram in Strain and Intraventricular Conduction Disturbances of the Left and Right Heart. Acta cardiol. **10:** 476 (Fasc. 5), 1955.

In 98 cases with electrocardiographic signs of right or left intraventricular block and right or left ventricular strain, vectorcardiograms were recorded according to the technic of Milanovitch and the 2 methods of registration were compared as to their clinical significance and diagnostic importance. The various vectorcardiographic patterns encountered are described as to the spatial location of loops and the direction of their development.

Both electrocardiography and vectorcardiography gave similar results regarding left ventricular hypertrophy and left bundle-branch block. Important differences were found in some cases with respect to right ventricular hypertrophy and right bundle-branch block. Thus, some electrocardiographic strain patterns behaved in the vectorcardiogram like bundle-branch block, while certain right bundle-branch block patterns showed, in the vectorcardiograms, alterations of the usual sense of loop rotation suggesting either concomitant right or left ventricular hypertrophy. Finally, in cases with incomplete and undetermined intraventricular block in the electrocardiogram, vectorcardiographic examination revealed normal loops in some, and the presence of right ventricular strain or right intraventricular block in others.

The authors conclude that vectorcardiography, while not suitable to replace scalar electrocardiography (and in fact proving sometimes to be the inferior method) offers the advantage of studying electric phenomena in a different and objective manner. It may demonstrate elements not obvious in the scalar electrocardiogram, particularly ventricular hypertrophy in the presence of ventricular conduction defects.

PICK

Tartulier, M., Tournier, A., and Guyot, R.: Death in Pulmonary Embolism. Electrocardiographic Study in 6 Anatomico-clinical Observations. Arch. mal. coeur **48:** 844 (Sept.), 1955.

The authors present electrocardiographic studies of the mode of cardiac death in 6 patients with fatal pulmonary embolism. In all instances the embolization was massive, obstructing 80 to 90 per cent of the pulmonary arterial bed.

Death was not instantaneous and usually occurred after a delay of several minutes. All electrocardiograms revealed the characteristic alterations of acute cor pulmonale as described by McGinn and White, with the development of right bundle-branch block. Following clinical death, electric activity of the heart persists for some time. The heart rate slows progressively, A-V block develops in addition to progressive intraventricular block, and sinus rhythm is replaced by an additional idioventricular rhythm that slows more and more while the ventricular complexes become deformed and atypical. In no case was there a sudden standstill or terminal ventricular fibrillation. These observations conform with experimental data and suggest that the terminal electrocardiographic alterations in fatal pulmonary embolization are due to anoxia of the myocardium.

PICK

Bayley, R. H.: The Normal Potential Variations on the Extremity, Back, and Precordial Electrodes with Reference to Central Terminals of Zero and Non-zero Potential. Am. Heart J. **50:** 694 (Nov.), 1955.

The author presents the electrocardiograms of 3 normal young adults and illustrates the manner in which a weighted central terminal influences the true potential variations V_R, V_L, V_F, and V_B at the corresponding electrodes when the unweighted central terminal is at a constant or 0 potential throughout the cardiac cycle and the manner in which the unweighted central terminal influences these potentials when the weighted terminal is at a constant or 0 potential throughout the cardiac cycle. Each subject required a central terminal of a different type in order that the terminal involved remain at a constant potential or equivalent 0 throughout the cardiac cycle. The unweighted terminal or T (r = 1 = f) has an error 3.4 times the error on the weighted terminal or TW (r = 1 = 2.6 f).

Studies in the living human subject are in considerable disagreement with those conducted upon homogeneous torso models. The author further states that standardization of vectorcardiographic leads at this time is premature and more energy should be directed at the solution of the lead problem than at recording and describing vectorcardiograms.

RINZLER

Pollack, P., Harmel, M. H., and Clark, R. E.: Estimation of Cardiac Output by the Ballistocardiograph During Thiopental-Nitrous Oxide-Oxygen Anesthesia. Anesthesiology **16:** 970 (Nov.), 1955.

Determinations of cardiac output by the Dock ballistocardiograph were performed before and after the induction of thiopental-nitrous oxide-oxygen anesthesia in 22 women requiring uterine curettage. No statistically significant changes were observed in the cardiac output after the induction of anesthesia. The use of the ballistocardiograph during anesthesia and operations is briefly discussed and the authors point out that the Ueda-Elliott accelerometer appears to be a more satisfactory instrument for use directly on the operating room table than the Dock ballistocardiograph.

SAGALL

HYPERTENSION

Floyer, M. A.: Further Studies on the Mechanism of Experimental Hypertension in the Rat. Clin. Sc. **14:** 163 (May), 1955.

The pathogenesis of hypertension was studied in a group of rats made hypertensive by partial constriction of one renal artery with a silver clip, and removal of the opposite kidney. In some animals, the clip was removed after a period of time, while in others the second kidney was extirpated.

In all instances, the blood pressure fell to normal on elimination of the partial constriction of the renal artery. When the second kidney was removed 3 days later, there was again a rapid rise in pressure. However, if the operation was performed 6 days later, there was only a moderately rapid rise. If the operation was delayed for 14 days, the hypertension slowly developed.

The results were used to support the concept that in the rat the kidney maintains normal blood pressure by inhibiting an extrarenal pressor mechanism. Nephrectomy or partial constriction of the renal artery prevents the kidney from exercising this inhibitory function, and hence hypertension develops.

ABRAMSON

McConn, R. G., Ford, R. V., Kent, B. M., Hughes, W. M., Dennis, E. W., and Moyer, J. H.: Administration of the Veratrum Alkaloids Protoveratrine and Cryptenamine in the Treatment of Hypertension: The Effect of Combination of Cryptenamine with Chlorpromazine and with Rauwolfia Serpentina. South. M. J. **48:** 774 (July), 1955.

The use of cryptenamine or protoveratrine alone

in the clinical treatment of hypertension is limited by the high frequency of nausea and vomiting and correspondingly low incidence of blood pressure response. The addition of the antiemetic agent chlorpromazine to cryptenamine permits an increase in the dosage of cryptenamine but does not increase the hypotensive-emetic ratio sufficiently to result in a significant reduction in blood pressure.

The combination of cryptenamine with *Rauwolfia serpentina* does not appear to have an additive hypotensive effect, and nausea and vomiting remain prominent. Chlorpromazine administered parenterally showed no dramatic benefit in preventing the nausea and vomiting caused by cryptenamine, being almost completely ineffective when an adequate blood pressure response was obtained.

BERNSTEIN

Bank, N.: The Relation of Malignant Hypertension to Periarteritis Nodosa in Humans. J. Mt. Sinai Hosp., New York **22:** 290 (Nov.-Dec.), 1955.

A group of 42 cases diagnosed at autopsy as periarteritis nodosa was reviewed. The group was heterogeneous, including 17 cases involving allergic mechanisms and 18 cases with no overt form of allergy. Of the latter, 10 presented the clinical syndrome of malignant hypertension while the other 8 had little or no hypertension.

The patients with malignant hypertension were relatively young and showed the normal features of malignant hypertension. In addition to the usual histologic picture they showed diffuse necrotizing arteritis of the periarteritis nodosa type. The "idiopathic" group, without significant hypertension, showed gross nodular aneurysms of medium-sized arteries and frequent involvement of the lungs—findings that differed sharply from the hypertensive group. Other differences were the more frequent evidences of partial healing and the absence of signs of malignant nephrosclerosis in the "idiopathic" group.

The author thinks that only cases of this "idiopathic" type deserve the title "periarteritis nodosa." The varieties of necrotizing angiitis should be classified, as suggested by Zeek, as: (1) hypersensitivity angiitis, (2) allergic granulomatous angiitis, (3) rheumatic arteritis, (4) periarteritis nodosa; and (5) temporal arteritis. The cases due to malignant hypertension should be classed as necrotizing arteritis secondary to malignant hypertension.

ENSELBERG

Smid, A. C., and DuShane, J. W.: Pheochromocytoma in Children. J. Dis. Children **90:** 81 (July), 1955.

A case report is presented of a 12-year-old boy who had hypertension of 5 months' duration. Blood pressure was recorded as 250 mm. Hg systolic and 160 mm. Hg diastolic. Accompanying this were headaches and convulsions. On examination, papilledema was present with narrowing of the arterioles without evidence of sclerosis. The eyeground changes suggested an "angiospastic episode" and the diagnosis of pheochromocytoma was suggested. This was confirmed by the phentolamine test. Successful surgery was carried out with removal of a 20-Gm. tumor from the left adrenal gland. Recovery was uneventful. A review of previously reported cases in children to the age of 14 is presented.

HARVEY

Achor, R. W. P., Hanson, N. O., and Gifford, R. W. Jr.: Hypertension Treated with Rauwolfia Serpentina (Whole Root) and with Reserpine. J. A. M. A. **159:** 841 (Oct. 29), 1955.

In a control study of 58 patients with essential hypertension, the effects of treatment with whole-root preparation of *Rauwolfia serpentina* compared with effects of treatment with reserpine revealed no significant differences in the 2 drugs. Forty per cent of the patients noted a satisfactory reduction of blood pressure. It is noted that a number of disagreeable side effects occur when rauwolfia preparations are used. Most are not serious; however, severe depressive reactions constitute a serious objection to the indiscriminate and unattended use of these drugs.

KITCHELL

Kurlander, A. B., Hill, E. H., and Enterline, P. E.: An Evaluation of Some Commonly Used Screening Tests for Heart Disease and Hypertension. J. Chron. Dis. **2:** 427 (Oct.), 1955.

The value of 4 commonly used screening tests—blood pressure, chest x-ray, electrocardiogram, and history—was determined individually and in combination in sorting out heart disease and hypertension from among 690 medically indigent, predominantly Negro, out-patients of a large general hospital. To do this, screening tests were administered, and subsequently all those subjects screened were given a completely independent cardiovascular examination.

In the screening procedure, blood pressure was taken in the sitting position (1 reading only) by a technician. A systolic pressure of 150 mm. Hg or higher, or a diastolic pressure of 90 mm. Hg or higher was considered positive. During the first half of the program, a physician questioned the subjects concerning cardiovascular symptoms. The physician covered 4 categories routinely: history of rheumatic fever, dyspnea, orthopnea, and chest pain. Later a series of questions was asked by a clerk. Standard lead I only, taken in a sitting position, was used to evaluate electrocardiographic abnormalities. Both 35 mm. and 70 mm. chest x-rays were used.

The value of the screening tests is expressed in terms of the percentage of the examinees with heart disease or hypertension so identified by the tests (sensitivity), and the percentage of the examinees

without heart disease or hypertension so identified by the tests (specificity). Blood pressure proved to be the most sensitive screening test, detecting 86 per cent of diagnosed heart disease or hypertension. Other tests did not differ much in sensitivity; they were much less sensitive than blood pressure, but varied widely in specificity. Blood pressure and chest x-ray appeared to be the best combination of 2 screening tests, picking up 91 per cent of diagnosed heart disease or hypertension while showing a specificity of 70 per cent. Blood pressure, chest x-ray, and electrocardiogram appeared to be the best combination of 3 tests. The percentage of previously unknown heart disease or hypertension (sensitivity) detected by individual tests ranged from 34 per cent for chest x-ray to 78 per cent for blood pressure. In general, specificity ratings for the various tests were quite poor, that is, a large per cent of individuals without heart disease or hypertension were screened as positive.

MAXWELL

Skelton, F. R.: Development of Hypertension and Cardiovascular-Renal Lesions during Adrenal Regeneration in the Rat. Proc. Soc. Exper. Biol. & Med. **90:** 342 (Nov.), 1955.

This report presents a simple technic for the production of a new type of experimental hormonal hypertension with cardiovascular renal lesions in rats sensitized by unilateral nephrectomy and salt administration. The method consists of unilateral adrenalectomy and contralateral adrenal enucleation. It demonstrates that such hypertension and cardiovascular-renal lesions can be produced without polydipsia and excessive sodium consumption and without alteration in the serum levels of sodium, potassium, or chloride. The results suggest that regenerating adrenal cortical tissue secretes increased quantities of cortical hormones and lend strong support to the hypothesis that increased adrenal cortical function is of fundamental importance in the pathogenesis of hypertension and cardiovascular-renal disease.

MAXWELL

Kolff, W. J., and Page, I. H.: Persistence of Experimental Renal Hypertension after Total Nephrectomy in Dogs. Am. J. Physiol. **182:** 531 (Sept.), 1955.

Nephrectomy was performed in dogs with experimental chronic renal hypertension. These animals were then kept alive by peritoneal lavage. The arterial hypertension persisted and was not related to blood urea levels. Sodium and potassium were normal and in most cases there was no overhydration. The authors suggest that early in experimental renal hypertension the renin-angiotonin mechanism is a primary pressor agency. However, in the chronic stage this same mechanism opposes the action of the kidney in maintaining normotensive levels. As a result one can consider that hypertension from renal deprivation and chronic renal hypertension are due to loss of renal factors that tend to produce a normal blood pressure.

OPPENHEIMER

Huntington, I., and Evans, J. A.: Results of Splanchnicectomy on Patients with Hemorrhagic Hypertensive Retinitis. New England J. Med. **253:** 398 (Sept. 8), 1955.

This report is concerned with the survival rate of patients with grade 3 or 4 eyeground changes who had undergone splanchnicectomy between 1935 and 1949. There were 189 patients followed for 4 to 19 years. Of the group, 147 had grade 3 and 42 had grade 4 hypertension. The survival curves were estimated to 10½ years. On the cumulative survival curve for grade 3 hypertension at intervals of 4½, 5½, 6½, 8½, and 10½ years, the survival for the surgically treated group was 72.8, 67.3, 61.9, 56.2, and 46 per cent as compared with an expected survival, as reported by Keith, Wagner, and Barker, of 22, 20, 10, 0, and 0 per cent respectively.

The survival rates in patients with grade 4 hypertension were contrasted with those reported by Palmer and Muench. The "relative survival rate" at 4½, 5½, and 6½ years was 47.8, 43.2, and 39.9 per cent in the surgically treated patients as compared with 5.7, 5.6, and 5.6 per cent in the medically treated group. The operative mortality was 2 per cent in the grade 3 and 6 per cent in the grade 4 patients. Three fourths of the patients in both groups reported that they felt well. Satisfactory reduction of the blood pressure was obtained in two thirds of the patients in grade 3 and four fifths of the patients in the grade 4 group. Thirteen nonfatal and 20 fatal cerebrovascular accidents occurred in both groups several months to years after operation in the 183 surviving patients, suggesting that splanchnicectomy does not reverse cerebral atheromatous disease. In both groups of patients the ability to concentrate urine to a specific gravity of at least 1.020 seemed to offer the best prognostic test for a good result.

The authors state that splanchnicectomy offers most to the patient with hemorrhagic eyegrounds and rapidly rising diastolic pressure with or without coincidental papilledema who is still young and has good kidney function and whose prognosis is statistically grave, with a 1 to 4 year life expectancy. If need be, a low-sodium diet and drug therapy may be used as adjunctive therapy and are more effective after sympathectomy.

ROSENBAUM

Friedman, S. M., Hardwick, D. F., and Hinke, J. A. M.: The Effect of Pitressin on Sodium Tolerance in Experimental Hypertension. Circulation Research **3:** 490 (Sept.), 1955.

In rats with experimental hypertension produced

by desoxycorticosterone acetate (DCA), by hydrocortone acetate (compound F), or by renal compression, sodium tolerance was studied. The administration of a standard test load of 100 mg. NaCl in 3 ml. of water by gavage confirmed previous studies that had shown that rats subjected to hypertension-inducing procedures develop an abnormal sodium tolerance. The curve is characterized by an acceleration in the rate of sodium excretion with or without an increase in the total amount excreted. Subcutaneous administration of pitressin in doses sufficient to lower the blood pressure in hypertensive rats was found to reverse the abnormality in sodium tolerance during the period of maximal blood pressure depression. This means that during the depression phase of pitressin action, active sodium retention is occurring rather than sodium loss. These experiments indicate a need for reinvestigation of the effects of pitressin on the renal regulation of salt metabolism.

SAGALL

Waldron, J. M., Reinhardt, D. J., III, Jenson, W. K., and Goldstein, F.: The Treatment of Diastolic Hypertension with a Fixed Combination of Hypotensive Drugs. Am. J. M. Sc. **230:** 551 (Nov.), 1955.

A combination of rauwolfia, protoveratrine, and phenoxybenzamine was administered orally to 75 hypertensive patients. Evaluation was made in only 38 patients who completed 6 months of treatment. Of this group, 19 patients were maintained at a normotensive blood pressure level. There were 9 additional patients showing a fair response; the remaining 10 responded unsatisfactorily or not at all. Poor responses occurred in patients with azotemia while those in Smithwick's group 1 responded satisfactorily. Advantages of the described therapy were ease of administration, minimum of severe side effects, a large percentage of satisfactory response, and the relative safety of the agents used. The disadvantages were failure of a sizable minority of patients to respond and the occurrence of minor annoying side effects.

SHUMAN

Minno, A. M., Bennett, W. A., and Kvale, W. F.: Pheochromocytoma: A Study of 15 Cases Diagnosed at Necropsy. Proc. Staff Meet., Mayo Clinic. **30:** 394 (Sept.), 1955.

The authors report 15 cases of pheochromocytoma in 15,984 consecutive necropsies performed at the Clinic from 1928 to 1951. Extra-adrenal chromaffin tumors were not included. The 15 cases are divided into 3 groups as follows: (1) malignant pheochromocytoma with metastasis; (2) pheochromocytoma with hypertension, either paroxysmal or persistent; and (3) benign pheochromocytoma found incidentally at necropsy with no clinical signs or symptoms. Grossly, the tumors varied in size from slight focal enlargement in the medulla to a mass weighing 3,167 Gm. However, the severity of the clinical symptoms was not related to the size of the tumors. Some of the smallest lesions produced the severest symptoms. The tumor usually consisted of polygonal cells of varying size that gave an alveolar appearance; the cells were supported by a fine connective-tissue stroma abundant in thin-walled blood vessels. Pheochromocytomas may occur at almost any age.

Pheochromocytoma was associated with neurofibromatosis in 1 case. This is the eleventh instance of association of these 2 disorders recorded in the available literature. Evidence of benign nephrosclerosis was present in 5 cases; malignant nephrosclerosis was present in 1 case and no demonstrable nephrosclerosis was evident in the remaining 9 cases. Death in 5 of these cases resulted from shock after incidental operations, suggesting the extreme danger of operative procedures in the presence of a pheochromocytoma. Necropsy revealed cardiac hypertrophy in 10 cases and pulmonary edema in 5 cases.

SIMON

Burgess, A. M.: Benign Essential Hypertension: Follow-up of 100 Patients Under Observation for from 18 to 34 Years. Ann. Int. Med. **43:** 742 (Oct.), 1955.

One hundred persons with essential hypertension were observed during the years 1923 to 1954. All had a systolic pressure of 180 mm. Hg or higher, or a diastolic pressure of 100 mm. Hg or higher, and had remained in good health for at least 8 years from the time of the first contact. By July 1, 1954, 74 had died, 18 were alive and well, and 8 could not be traced. Thirty-two patients were 50 years of age or younger when first observed to have hypertension. Of this group, 17 had died, 13 were alive, and 2 could not be traced. Sixty-eight patients were over 50 years of age when first seen. Of this group, 55 had died, 7 were alive, and 6 could not be traced. None of the patients had symptoms directly attributable to hypertension. Some dizziness and occasional headaches were mentioned by the older group, in about the same proportion as occurs in others of the same age. Systolic pressures of over 300 mm. Hg were seen in 5 patients, but did not appear to cause any symptoms. No patients in this group developed malignant hypertension.

WENDKOS

PATHOLOGY

Jones, G. P., and Julian, D. G.: Left Atrial Tumour Simulating Mitral Stenosis. Brit. M. J. **4935:** 361 (Aug.), 1955.

Primary cardiac tumors are quite uncommon, but are now being reported with increasing frequency. On occasion, surgical removal may be possible when mechanical obstruction occurs, but preoperative diagnosis is difficult. The case described in this article manifested some of the features of rheumatic

mitral stenosis, but valvular disease was not detected at operation. The diagnosis of a localized cardiac tumor, usually a myxoma, producing obstruction is now of more than academic interest. Anomalous signs such as were found in this case may permit a preoperative diagnosis and so facilitate radical removal in a planned operation. It would seem that a short history of symptoms, and fairly rapid deterioration, combined with absence of the classical radiologic appearances of mitral stenosis, are the only helpful indications of the presence of a left atrial tumor.

BERNSTEIN

Sweetham, W. P., and Sykes, C. G. W.: Acute Benign Pericarditis in Infancy. Arch. Dis. Childhood **30:** 467 (Oct.), 1955.

A case of acute benign pericarditis in a 7-week-old infant is presented. The illness was preceded by a mild infection of the upper respiratory tract. Signs of pericardial tamponade supervened and 150 ml. of serous fluid was removed from the pericardial sac. Bacteriologic studies were unrevealing. No evidence was found for tuberculosis or rheumatic fever. The infant recovered uneventfully. A discussion of this syndrome is presented.

HARVEY

Theret, C.: Histological Study of the Myocardial Lesions in Bronze Cirrhosis. Arch. mal. coeur **48:** 937, 1955.

In clinical cases as well as in rabbits injected intravenously with excess blood and polyvinyl pyrrolidine, the Q bands of the myocardial fibrils showed a tendency to become transformed into dark disks composed of granules containing iron. These changes indicate that bronze cirrhosis is accompanied by a profound disturbance in the physicochemical balance in the myocardial fibril and explain the cardiac failure refractory to digitalis observed in many clinical cases.

LEPESCHKIN

Zayas Portela, E. I., Gonzalez Herrera, R., and Larraondo Nuñez, F.: Myocarditis in Diphtheria. A Study of 17 Cases. Rev. cubana cardiol. **16:** 349, 1955.

Of 838 patients with diphtheria, 44 died and an autopsy was performed on 17 of these. Histologic study disclosed myocarditis in all cases. Fifty-nine per cent of the cases died between the second and the seventh day of the disease. The most frequent manifestations were tachycardia after disappearance of fever or bradycardia and shock. Heart failure or murmurs did not appear. Of the 8 patients with electrocardiograms, 2 showed complete A-V block, 2 bundle-branch block, and 2 showed deep depression of S-T in the left precordial leads; 4 showed only sinus tachycardia.

LEPESCHKIN

Coleman, P. N.: A Case of Dissecting Aneurysm in a Child. J. Clin. Path. **8:** 313 (Nov.), 1955.

A case of dissecting aneurysm of the aorta due to medial degeneration is described in a girl aged 10 years. The rarity of dissecting aneurysms in children is stressed. The etiology of medial degeneration in the young is probably congenital. Medial degeneration is frequently associated with other developmental defects, particularly coarctation and Marfan's syndrome.

MAXWELL

Morse, S. I., Darnell, J. E., Jr., Thomas, W. A., and Glaser, R. J.: Cardiac Lesions in Rabbits After Pharyngeal Infections with Group A Streptococci. Proc. Soc. Exper. Biol. & Med. **89:** 613 (Aug.-Sept.), 1955.

Thirty-five rabbits were subjected to pharyngeal infections with streptococci. Twenty-nine were infected once and 6 underwent multiple infections. In almost all of these rabbits the following occurred: myocardial lesions characterized by muscle necrosis, disruption of collagen, replacement fibrosis and infiltration with histiocytes, lymphocytes, Anitschkow myocytes, and occasional multinucleated giant cells. These lesions could be demonstrated as early as 24 hours following a first infection and indicated that a nonimmunologic mechanism might be responsible, which raises the question as to whether human rheumatic fever is a disease due solely to an antigen-antibody reaction.

MAXWELL

Wenger, D. S.: Does Uncomplicated Pleuropericardiomediastinitis Result in Myocardial Hypertrophy? Surgery **38:** 513 (Sept.), 1955.

An experimental study using 10 dogs was undertaken for the purpose of determining whether or not pleuropericardiomediastinitis causes cardiac hypertrophy. Mediastinopericarditis is a condition in which the parietal pericardium is firmly bound to adjacent structures by fibrous adhesions. Uncomplicated mediastinopericarditis does not include adhesions between the epicardium and parietal pericardium, but involves only the parietal pericardium and mediastinum, pleurae, and diaphragm. In theory, the work of the myocardium is not increased and, therefore, hypertrophy would not result.

In order to produce pericardiomediastinitis, talcum powder was liberally sprinkled over the pericardium and adjacent structures. The dogs were sacrificed from 6 months to 1 year later. At autopsy, the heart weights were not increased and there were no demonstrable histologic changes in the muscle fibers.

MAXWELL

Grosse-Brockhoff, F., and Schreiber, H. W.: Angiosarcoma of the Pericardium. Ztschr. Kreislaufforsch. **44:** 866 (Nov.), 1955.

The authors report a case of angiosarcoma of the

pericardium in a 22-year-old female, verified at autopsy. Clinically, the patient presented at first a picture of a bilateral pleural effusion and later that of exudative pericarditis with progressive obstruction of venous return. Roentgenologically, the suspicion of a tumor of the pericardium was raised early in the course of the disease. Repeated pericardial taps were negative in that merely blood could be aspirated. The entire course from the onset of the symptoms to death extended over a period of 1¼ years. According to the author this is the fifth reported case of a tumor of this sort.

PICK

DeMuth, G. R., and Landing, B. H.: The Occurrence and Possible Significance of Generalized Vascular Disease in Idiopathic Cardiac Hypertrophy. Am. Heart J. **50:** 643 (Nov.), 1955.

The case history of a 2½-month-old white male with idiopathic cardiac hypertrophy is presented. At autopsy, many muscular arteries in a number of organs showed mural thickening, predominantly by hypertrophy of the muscular tissue of the media. To assess the significance of these vascular lesions, measurements were made of the thickness of the medias of muscular arteries: 107 were measured in 4 patients with idiopathic cardiac hypertrophy, 111 in 5 patients with endocardial sclerosis, and 111 in 4 control patients. Widespread arterial medial hypertrophy and focal intimal fibrosis were demonstrated in the patients with idiopathic cardiac hypertrophy. Similar but less severe lesions occurred in patients with endocardial sclerosis. The authors suggest that it is possible that the 2 conditions are, therefore, consequences of the same cause and are, in a sense, both variations of a disease that produces widespread thickening of vascular walls.

RINZLER

Dimond, E. G., Allen, F., and Moriarity, L. R.: The Clinical Picture of Endocardial Fibroelastosis Infantile and Childhood Type. Am. Heart J. **50:** 651 (Nov.), 1955.

Of 154 autopsies on children under 10 years of age done at the University of Kansas Medical Center, 9 show endocardial fibroelastosis, which made this disease the most common cardiac condition associated with death in children below the age of 10 in their series. Clinically, a newborn, an infant, or a young child develops respiratory distress manifested by cough, noisy breathing, and tachypnea—all signs of heart failure. Death may be immediate. If an x-ray of the chest is taken, an enlarged, globular heart is found. A tender, large liver and peripheral edema may be found. The electrocardiogram may show sinus tachycardia, T wave depression, flattening or inversion, P-R interval prolongation, and widening of the QRS complex. The progress of the disease is generally downhill. Some children may live for as long as 2 or 3 years.

RINZLER

Hays, F. B., and Boggan, W. H.: Rupture of Aortic Valve Cusp Attachment Due to Cystic Medionecrosis of the Aorta: a Case Report with Necropsy Findings. Ann. Int. Med. **43:** 1107 (Nov.), 1955.

A 27-year-old Negro without previously known heart disease developed a sudden episode of heart failure from which he died 3 months later. During life, a musical diastolic murmur and a rough systolic basal murmur were audible and graphically recorded. At autopsy, the heart was dilated and hypertrophied. The common attachment of the posterior and right anterior valve cusps had separated from the site of insertion in the aorta. Because of the loss of attachment, there was sagging of the free border of the involved cusps with rolling of the ruptured attachment toward the center of the aortic valve opening. In the aorta, there was an irregular area of scarring, beginning just above the aortic ring and extending distally for 8 cm., that involved the entire circumference of the aorta. No ulceration was present in this area, and elsewhere the intima was normal in appearance. Microscopic sections of the aorta in the area of the torn valve revealed destruction of the elastic tissue and cystic degeneration. Sections from the area of scarring at the root of the aorta showed thickening of the wall, due predominantly to increased thickness of the adventitia and the media. The adventitia was edematous, and a mild chronic inflammatory process was present. Numerous thin-walled vessels penetrated into the media from the adventitia. The degeneration of the media with vacuolation of the muscle fibers was conspicuous. Chromotropic substance was seen in special stains, as were loss and separation of elastic fibers. This is considered to be the first documented case of ruptured aortic valve cusps resulting from congenital cystic medionecrosis of the aorta.

WENDKOS

PATHOLOGICAL PHYSIOLOGY

Bishop, J. M., Donald, K. W., and Wade, O. L.: Circulatory Dynamics at Rest and on Exercise in the Hyperkinetic States. Clin. Sc. **14:** 329 (May), 1955.

The authors studied the effect of exercise on cardiac output in patients with anemia, thyrotoxicosis, and arteriovenous fistula.

In the 7 patients with anemia, the resting cardiac outputs were all above 4.61/min./M.^{2} and in each instance there was an abnormally high cardiac output in response to exercise. The results suggested that in the hyperkinetic state exercise was associated with an increase in stroke volume rather than an elevation of the heart rate.

The patients with thyrotoxicosis and arteriovenous fistula also showed abnormally high cardiac output in response to exercise.

ABRAMSON

Catchpole, B. N., Hackel, D. B., and Simeone, F. A.: Coronary and Peripheral Blood Flow in Experimental Hemorrhagic Hypotension Treated with l-Norepinephrine. Ann. Surg. **142:** 372 (Sept.), 1955.

An experimental study was performed on dogs to determine the effect of l-norepinephrine on coronary and peripheral blood flow in the presence of hemorrhagic hypotension. Coronary blood flow was measured by the nitrous oxide desaturation technic, and peripheral blood flow was determined by the method of venous occlusion with a bonded strain gage and a direct-writing oscillograph.

During the period of hypotension produced by bleeding, the rate of blood flow through the paw fell, but no significant change in coronary circulation was produced. When the hypotension was corrected to normotension by means of l-norepinephrine without altering the oligemia, the rate of flow through the paw remained unchanged, while flow through the coronary vessels rose to very high levels. However, cardiac output did not increase.

In contrast, the transfusion of blood restored coronary vascular resistance toward normal. It increased the rate of blood flow in the periphery and decreased the peripheral vascular resistance temporarily.

The authors found that the correction of the hypotension by l-norepinephrine did not result in a higher rate of survival as compared with a control series of dogs not receiving this drug.

ABRAMSON

Clowes, G. H. A., Jr., Hopkins, A. L., and Simeone, F. A.: A Comparison of the Physiological Effects of Hypercapnia and Hypoxia in the Production of Cardiac Arrest. Ann. Surg. **142:** 446 (Sept.), 1955.

Experimental severe respiratory acidosis and hypoxia were produced in dogs in order to evaluate their role in initiating cardiac arrest. The respose to severe hypercapnia induced by inhalation of 55 per cent CO_2 caused a marked but transient hypotension and bradycardia, followed by a return of pulse and blood pressure nearly to control levels and then a second decline. The effect of severe hypoxia was an immediate elevation of blood pressure or pulse rate or both, followed by bradycardia. However, the hypertension continued.

The authors pointed out that in asphyxia, CO_2 accumulation and oxygen want combined to produce cardiac arrest, but the mode of action of the 2 factors was different. Section of the vagi did not materially affect the response to 55 per cent CO_2 or 1 per cent oxygen inhalation; however, following sympathectomy and adrenalectomy, the inhalation of a mixture of both gases caused early cardiac arrest.

ABRAMSON

Duff, F., Patterson, G. C., and Whelan, R. F.: The Effect of Intra-Arterial Antihistamines on the Hyperaemia Following Temporary Arrest of the Circulation in the Human Forearm. Clin. Sc. **14:** 267 (May), 1955.

The authors studied the effect of intra-arterial injection of antihistamines on the hyperemia of the human forearm produced by various periods of circulatory arrest. It was found that these substances did not affect the blood response to 3 minutes of occlusion but did reduce the magnitude of increase in blood flow following 5 or more minutes of circulatory arrest. The antihistamines nearly or completely abolished the augmentation in local circulation produced by the intra-arterial injection of histamine.

The reduction of hyperemia from prolonged periods of occlusion produced by antihistamines was interpreted as indicating that the latter were antagonizing some dilator substance released in the tissues, most likely histamine. However, it was believed that the production of such a substance under these circumstances was the consequence of tissue damage.

It was concluded that the release of histamine did not appear to play any major role in the phenomenon of reactive hyperemia.

ABRAMSON

Love, A. H. G.: The Rate of Blood Flow and the Oxygen Saturation of the Effluent Blood Following Contraction of the Muscles of the Human Forearm. Clin. Sc. **14:** 275 (May), 1955.

The effect of exercise on the oxygen content of venous blood was studied in 7 healthy young men. At the same time blood flow determinations were made by the venous occlusion plethysmographic method.

During rhythmic contractions of the muscles of the human forearm, the oxygen saturation of the effluent deep venous blood fell below the resting values. During sustained contractions it usually fell, but at times it rose. Following the contractions, whether rhythmic or sustained, the oxygen saturation rose considerably above the resting level and then slowly declined to basal levels.

The raised saturation of the venous blood was interpreted as indicating an increased oxygen tension in the veins and in the capillaries. The results did not exclude the possibility of local anoxia as a cause of the increased blood flow after contraction of skeletal muscle, although it was considered as an unlikely major factor.

ABRAMSON

Shanks, R. G.: The Effect of Venous Congestion on the Rate of Heat Elimination from the Fingers. Clin. Sc. **14:** 285 (May), 1955.

The author studied the effect of producing venous congestion of the fingers of normal subjects on the rate of heat elimination. With a pressure between that in the veins and the diastolic pressure

in the arteries, the venous outflow from the hand was temporarily arrested until the pressure in the vessels distal to the cuff became slightly greater than the cuff pressure. It was found that heat elimination was reduced in direct proportion to cuff pressure and approached zero when the cuff pressure reached the mean arterial pressure.

On the basis that heat elimination was a reasonably reliable measure of blood flow, the results were considered to indicate that there was no substantial change in peripheral resistance in the finger during venous congestion.

ABRAMSON

Walder, D. N.: The Relationship Between Blood Flow, Capillary Surface Area and Sodium Clearance in Muscle. Clin. Sc. **14:** 303 (May), 1955.

An attempt was made to evaluate the use of clearance of radioactive sodium in muscle as a method of measuring blood flow. The isolated skinned hind limbs of rabbits and cats were used, the perfusion fluid consisting either of the animal's own heparinized blood or of alkaline Ringer-Locke solution. Blood flow studies were also performed in human subjects, by means of the clearance method and plethysmographic technic.

At low rates of flow following exercise, clearance of radioactive sodium ceased, possibly because of shunting either through arteriovenous direct capillaries or through larger arteriovenous communications. Above the "critical" level of blood flow, changes in clearance of radioactive sodium were considered to be linearly related to alterations in blood flow.

It was concluded that the clearance rates could be used to estimate blood flow during violent exercise, as contrasted with the plethysmographic method, which was only applicable in the immediate postexercise period. However, values for the clearance rate of radioactive sodium from muscle at rest were considered to give little information regarding blood flow under these circumstances.

ABRAMSON

Born, J. V. R., Dawes, G. S., Mott, J. C. and Rennick, B. R.: The Relief of Central Cyanosis Caused by Pulmonary Arterio-Venous Shunts by Construction of an Artificial Ductus Arteriosus. J. Physiol. **130:** 167 (Oct.), 1955.

In anesthetized dogs, cyanosis due to an A-V shunt (caused by obstruction of one or more bronchi) was partly relieved by a created ductus arteriosus. This can be explained very simply by recirculation of the cyanosed arterial blood, which passes through the ductus to pick up more oxygen until a new equilibrium is established. When the artificial ductus is opened, blood flows through it from aorta to pulmonary trunk, pulmonary arterial pressure is raised, and the oxygen saturation of pulmonary arterial blood is also substantially increased. The same principle holds true for correction of nonuniform pulmonary defects of an intractable nature, such as widespread and inoperable bronchiectasis or emphysema. The construction of an artificial ductus in such cases is theoretically helpful even if the practice is found to be inadvisable owing to lack of reserve capacity in the remaining functional alveoli, to existing pulmonary hypertension or to consequent right heart failure.

AVIADO

Howell, F. R., and Richards, T. G.: The Determination of Pressure-Volume Changes in the Femoral Tree of the Cat in Relation to Vascular Tonus and the Resistance Offered to Blood Flow. J. Physiol. **130:** 414 (Nov.), 1955.

Pressure-volume curves for the femoral tree of the anesthetized cat were obtained after the intra-arterial administration of epinephrine and norepinephrine. Small doses of epinephrine reduced the pressure at which the blood flow ceased, but had little effect upon the total volume change. These results may be explained by vasoconstriction of skin vessels (with an accompanying loss of potential volume change), and a simultaneous vasodilatation of muscle vessels (which would increase the potential volume change and would balance the volume change of skin vessels).

On the evidence presently available, it cannot be said that for the pressure-volume curves in general, the portion showing rapid volume changes represents only massive closure of minute peripheral vessels. After the administration of norepinephrine and larger doses of epinephrine, vessels that normally play a negligible part in resistance to flow become constricted and may offer a relatively large resistance.

Increased vascular tone was accompanied by a marked diminution of the rate of change of vascular volume with change of pressure and by an increase in the pressure at which blood ceased to flow.

AVIADO

Klopper, P. J.: Splenic Function in Relation to Blood Pressure Changes Evoked by Stimulation of the Cerebral Cortex. J. Physiol. **129:** 547 (Sept.), 1955.

Fluctuations of arterial pressure were caused by electric stimulation of specified areas on the ventral and dorsal surfaces of the frontal lobe and temporal lobe of the cat. The spleen appeared to have considerable influence on such changes in blood pressure, since extirpation reduced the blood pressure response. This effect is brought about by releasing an amount of blood into the circulation amounting to about 3 per cent of the total circulating blood volume. The physiologic significance of cortical centers affecting blood pressure and splenic volume is not known.

AVIADO

Perry, W. L. M., and Reinert, H.: On the Metabolism of Normal and Denervated Sympathetic Ganglion Cells. J. Physiol. **130:** 156 (Oct.), 1955.

After chronic preganglionic denervation of the superior cervical ganglion of cats, methonium compounds no longer block but potentiate the effects of injected acetylcholine, and in some 50 per cent of experiments, themselves cause stimulation of the ganglion cells (as judged by contraction of the nictitating membrane). The same changes in response to methonium compounds occur in normal ganglia perfused with modified Locke's solution containing a reduced concentration of potassium. The addition of amino acids to the Locke's solution perfusing a ganglion reverses such effect of methonium as long as glucose is present. It is suggested that this reversal of action of methonium compounds (on denervated ganglion) is due to a fall in intracellular potassium concentration of ganglion cells and a consequent inhibition of oxidative metabolism. This is restored by amino acids possibly because of their "potassium-carrier-function." It is further suggested that the methonium compounds may act by blocking the oxidative metabolic pathway.

AVIADO

Wadsworth, G. R.: Recovery from Acute Hemorrhage in Normal Men and Women. J. Physiol. **129:** 583 (Sept.), 1955.

The effects of a sudden loss of about 8 per cent of the blood volume were investigated by repeated measurements of blood hemoglobin concentration, plasma specific gravity, and reticulocyte counts. When account was taken of normal variation in hemoglobin levels, recovery was apparently complete in 3 to 4 weeks. Isolated measurements of hemoglobin concentration could give false information of the extent of blood loss, the stage of recovery from hemorrhage, and whether bleeding was continuing or had ceased. More reliable information about these points might be obtained from repeated daily estimations of hemoglobin concentration accompanied by reticulocyte counts. There was no evidence that women were at a disadvantage compared to men in dealing with a sudden loss of blood.

AVIADO

Hirsch, M., Koch, D., Krenkel, W., and Schneider, M.: The Latency of Recovery of the Brain of Mammals in Ischemia and the Meaning of a Rest Circulation. Pflüger's Arch. **261:** 392 (Oct.), 1955.

The isolated head of cats was used to measure the time interval of recovery of the spontaneous electric potential of the brain after exposure to ischemia of varying severity and duration. If the blood flow were not less than 12 per cent of normal, even on long reduction of flow, no changes in electric potential were recorded. At 12 per cent of normal flow there was almost complete paralysis of function, but recovery was possible for a very long time. Only at even lower levels the latency of recovery after correction of ischemia was longer, and if ischemia was prolonged recovery was not obtained, and irreversible changes were produced.

CALABRESI

Hort, W.: Quantitative Investigation on the Capillary Supply of the Cardiac Muscle of Adult and Old Age in Hypertrophy and Hyperplasia. Virchows Arch. path. anat. **327:** 560 (Nov.), 1955.

The capillary bed of the cardiac muscle is studied by periodic acid-leucofuchsin Schiff staining in 36 hearts of various ages and weights. In accord with previous observations, it is found that in the papillary muscles and also in the wall of the left ventricle there is approximately 1 capillary per muscle fiber. No significant difference is found among adult and old persons, nor in hypertrophic hearts. Following Linzbach, the author maintains that when the hypertrophy reaches a critical weight the cardiac fibers increase in number; as the ratio fibers to capillaries do not change, it is concluded that the number of capillaries also increases. The ratio in the papillary muscles of the right ventricle is approximately equal to that of the left ventricle, although the meshes are more narrow. The variable thickness of the endocardium and the structural characteristics of the subendocardial myocardium and its capillary vessels are briefly described.

CALABRESI

Bouchard, F., Laurens, P., and Servelle, M.: Intracardiac Pressures During Mitral Commissurotomy. Arch. mal. coeur **48:** 1065 (Nov.), 1955.

Intracardiac pressures were registered by means of a needle 0.6 mm. in diameter, connected to a frequency modulation manometer with a resonant frequency of 120 cps. The left atrial pressure fell after commissurotomy in all cases of pure stenosis, but the fall was much smaller or absent in those with additional regurgitation. The left ventricular pressure rose in a minority of the cases. The pulmonary pressure usually fell, but in 2 cases it remained high in spite of an appreciable fall in left atrial pressure; the lung consistency in these cases was not greater than in those showing a satisfactory fall of pressure. A normal configuration of the left atrial pressure curve was found in only 3 cases with systolic pressures less than 30 mm. Hg. In the first pathologic type, the *a* and *c* waves are separated and very tall, in the second type *a* is fused with *c* and a V-shaped *x* depression separates them from the very tall *v* wave.

In the third type the depression *x* is U-shaped, while in a fourth type *a*, *c*, and the tall *v* are fused and *x* very small. In the 2 last-mentioned types the mitral valves were found flexible in all cases. In the presence of mitral regurgitation the first type shows a small *a* fused with a large *c* and followed by a tall *v*, without an *x* depression; in this type no change was found after commissurotomy. In the second type *a* is

taller than *c* and well separated from a tall *v*; *v* decreased after commissurotomy.

LEPESCHKIN

Breda, F., and Papagni, L.: Study of Hepatic Pulsation by Means of Pneumoperitoneum and Roentgen Kymography under Normal and Pathological Circulatory Conditions. Folia cardiol. **14:** 297, 1955.

Roentgen kymograms of the right hepatic border in left lateral position after penumoperitoneum reflect true hepatic pulse better than any other method and also represent atrial pressure better than kymograms of the atrial border, since they are least of all influenced by transmitted cardiac pulsations. They were registered in 24 persons; those without heart disease show only small presystolic pulsations. Systolic pulsations were found only in cases with tricuspid insufficiency and in some cases of aortic insufficiency. In the latter they are of small amplitude and probably represent pulsation of the hepatic arteries. In 2 cases of tricuspid stenosis the presystolic pulsations were much larger than those appearing in normal subjects.

LEPESCHKIN

Michel, D., Herbst, M., Hartleb, O., and Bock, K.: The Diagnostic Significance of the "Oxygen Step" in Cardiac Catheterization. Ztschr. Kreislaufforsch. **44:** 902, 1955.

Statistical analysis of 50 cases showed that diagnosis of atrial septal defect or transposition of the pulmonary veins can be made if the oxygen concentration of the right atrium is at least 2.5 volume per cent higher than that of the average in the superior and inferior venae cavae. A ventricular or aorticopulmonary septal defect or a persistent ductus becomes probable if the difference in oxygen concentration between the right ventricle and atrium or between the pulmonary artery and right ventricle exceeds 1.7 volume per cent. If averages of 3 to 5 blood samples are taken, the difference necessary for the diagnosis is only ⅔ that mentioned above. A shunt can also be diagnosed if the greatest difference between 5 samples taken at the same position exceeds 1.3 volume per cent in the right atrium, 1.2 in the right ventricle, and 0.9 in the pulmonary artery.

LEPESCHKIN

Haller, J. A., Jr., and Morrow, A. G.: Experimental Mitral Insufficiency. Surgery **38:** 518 (Sept.), 1955.

A method of measuring transbronchial left atrial pressures in dogs is described and data are presented that were obtained in dogs with acute and chronic mitral insufficiency. When a needle is passed through the anterior inferior wall of the left main stem bronchus approximately 2 cm. below the carina, the needletip lies free in the atrium in nearly all instances. Left atrial pressures were obtained in normal dogs prior to thoracotomy. These dogs were then operated upon and direct left atrial pressure measurements made with the same recording system. Mitral regurgitation was produced through a left auricular approach by cutting of valve leaflets and through a left ventricular approach by severance of chordae tendineae. Transbronchial left atrial pressure measurements were made in the immediate and late postoperative survival periods. Specific measurement was made of the atrial systolic pressure or A wave, the early diastolic pressure or X wave, and the last positive pressure in late atrial diastole, the V wave.

In 10 normal dogs the A and V waves were equal. The A-wave pressures were between 4 and 10 mm. Hg with an average of 7.8 mm. Hg. The X-wave pressures were between 1 and 3 mm. Hg with an average of 1.3 mm. The calculated average left atrial mean pressure was 3.5 mm. Hg. In 18 dogs with mitral regurgitation the V wave was uniformly elevated and always higher than the A wave. The range of V-wave pressures was between 9 and 35 mm. Hg. The range of X-wave pressures was between 0 and 17 mm. Hg. The average V-wave pressure was 16.6 mm. Hg and average X-wave pressure was 4.2 mm. Hg. The average left atrial mean pressure was 8.1 mm. Hg. The most striking change in the left atrial pressure curve after regurgitation is in the V-wave component. This wave is uniformly elevated and always shows a sharp upslope beginning prior to the onset of ventricular ejection and reaching its zenith with the beginning of isometric relaxation.

The authors cite a single example to illustrate the possible use of the transbronchial method of recording left atrial pressures in studying changing lesions of the mitral valve. Serial pressures taken in 1 dog revealed a gradual change of the left atrial pressure towards normal. Sacrifice of the dog revealed complete healing of the operative defect in the mitral cusp.

MAXWELL

Badeer, H.: Role of Hypoxia in Hypothermic Cardiac Arrest in the Heart-Lung Preparation. Am. J. Physiol. **183:** 119 (Oct.), 1955.

Heart-lung preparations were arranged to measure total coronary flow. The temperatures at which ventricular fibrillation caused cardiac arrest were 19.6 C. when air was used and 20.3 C. if oxygen (100 per cent) was used to inflate the lungs. When air inflation was practiced, the coronary flow at the time of fibrillation was 27 per cent greater than control flows just before hypothermia began. In the case of oxygen, the terminal flow was 36 per cent greater than controls; but in this case a pump was used to elevate aortic pressures. Thus, coronary flow was adequate at the end of the experiment when oxygen was used. This gas did not change the critical tem-

perature for hypothermia. Hypoxia does not appear to have a role in cardiac arrest during hypothermia.

OPPENHEIMER

Koletsky, S., and Klein, D. E.: Reversibility of Tourniquet Shock with Massive Saline Therapy. Am. J. Physiol. **182:** 439 (Sept.), 1955.

In this study life was prolonged in terminal tourniquet shock but death was not prevented by a single large saline infusion. However, if a quantity of saline was used equal to 15 per cent of body weight via peritoneal and intravenous routes, the terminal state of tourniquet shock was reversed in 75 per cent of cases. Elevation in tissue tension probably opposed continued fluid loss. Restoration of sodium in extracellular fluid and blood volume also played a role.

OPPENHEIMER

Mandel, M. J., Vidt, D. G., and Sapirstein, L. A.: Disappearance of Para-Amino Hippuric Acid from the Plasma of the Dog after Single Intravenous Injection. Am. J. Physiol. **182:** 428 (Sept.), 1955.

Excretory clearances of para-amino hippuric acid (PAH) determined by disappearance curves and infusion clearances of PAH were compared. In 11 of fifteen cases they were found to be in good agreement. The total volume in which PAH is distributed is somewhat larger than the volume of extracellular fluid. The authors point out the possibility of using a single injection of PAH to determine renal plasma flow when bladder and infusion clearances cannot be obtained.

OPPENHEIMER

Cournand, A.: The Mysterious Influence of Unilateral Pulmonary Hypoxia upon the Circulation in Man. Acta cardiol. **10:** 429 (Fasc. 5), 1955.

The effects of unilateral hypoxia upon the pulmonary circulation were studied in man with the help of a new method combining bronchospirometry, cardiac catheterization, and arterial puncture. This method permits simultaneous determination of the total pulmonary blood flow, flow through each lung separately, and of pulmonary arterial pressures. The experiments were designed in such a manner as to differentiate influences of local pulmonary vascular resistance, increase of pulmonary blood flow, and of arterial hypoxemia.

The analysis of the data revealed that elevation of the pulmonary vascular resistance can be excluded as a factor responsible for pulmonary hypertension developing in the course of breathing of a hypoxic mixture. The most likely cause of the pressure elevation appears to be an increase in pulmonary blood flow in association with some other hemodynamic alterations related to severe arterial hypoxemia, probably displacement of blood from the systemic to the pulmonary vascular bed.

PICK

Kreuziger, H., Heinecker, R., and Kemper, F.: The Effect of Cigarette Smoking upon the Circulation. Ztschr. Kreislaufforsch. **44:** 879 (Nov.), 1955.

The authors performed cardiodynamic investigations during cigarette smoking in normal fasting subjects (17–49 years old). The tests consisted of recording the electrocardiograms and simultaneous pulse curves of the carotid and femoral arteries. The pulse curves were then submitted to analysis according to methods developed by Broemser and Ranke.

In supine position, 7 of 8 test subjects developed objective sympathotonic reactions while subjective complaints were minimal or absent. In the standing position, 13 out of 17 cases complained of dizziness, nausea, visual disturbances, and perspiration, and in 10 this preceded syncope. The cardiodynamic data revealed orthostatic insufficiency with reduction of venous return and minute output in the presence of increase of peripheral resistance. The electrocardiogram showed nonspecific abnormalities of the ST-T. Subsequent to recovery there was a transient inhibition of diuresis. Only 4 persons reacted with sympathotonic alterations without subjective sensations.

The investigations serve to demonstrate the considerable circulatory alterations that can be induced acutely by cigarette smoking. They are consistent with the 2 known pharmacologic effects of nicotine, viz., initial sympathetic stimulation with release of epinephrine, followed by paralysis of vegetative ganglia.

PICK

PHARMACOLOGY

Schroeder, H. A., and Perry, H. M.: Psychosis Apparently Produced by Reserpine. J. A. M. A. **159:** 839 (Oct. 29), 1955.

Five patients developed psychotic behavior with agitated depression while receiving reserpine. They recovered completely when the drug was discontinued. In 3 of these 5 individuals the symptoms consisted of increased nervousness, insomnia, agitation, and depression. Continuation of the therapy with the drug resulted in sporadic but increasingly recurring bouts of paranoia with suicidal tendencies followed by lucid intervals with clear insight. Recovery was slow and took from 1 to 2 months. These patients had not been known to have such behavior prior to taking the drug.

KITCHELL

Kaunitz, H.: The Biological Antagonism between Sodium and Potassium. Exper. Med. & Surg. **13:** 53 (Nov. 1), 1955.

This paper is included in an issue dedicated to Rudolf Keller and deals to a large extent with Keller's contributions to the problem of mineral metabolism in connection with his studies on the electropotential differences between cells and blood.

The author then gives more historical data on mineral metabolism. Early observations suggested that the normal kidney supports the maintenance of normal serum sodium chloride levels and preserves the potassium stores of the organism. Loeb, in 1932, demonstrated a function of the adrenal cortical hormone with respect to sodium and potassium diametrically opposed to that of the kidney. Studies of the sodium and potassium content of the tissues under various pathologic conditions followed. The biological antagonism of sodium and potassium is shown by the fact that potassium favors diuresis while sodium leads to water retention. The 2 minerals have an antagonistic action on the neuromuscular equilibrium in that sodium stimulates and potassium inhibits muscular activity. Other antagonistic actions are further described.

RINZLER

Bellet, S., Wasserman, F., and Brody, J. I.: Molar Sodium Lactate. Its Effect in Complete Atrioventricular Heart Block and Cardiac Arrest Occurring During Stokes-Adams Seizures and in the Terminal State, New England J. Med. **253:** 891 (Nov. 24), 1955.

The authors report upon the effect of administration of molar sodium lactate to patients with complete atrioventricular heart block without symptoms, to patients with complete atrioventricular heart block and Stokes-Adams seizures, and to patients with terminal cardiac arrest. In patients with asymptomatic complete heart block, the intravenous administration of 120 ml. of molar lactate in 10 to 15 min. increased the heart rate appreciably in 10 of 12 cases. Transient ventricular extrasystoles or coupling due to extrasystoles occurred in 4 of a total of 46 patients in whom this treatment was used. In some patients in whom extrasystoles were present prior to treatment, the ectopic beats became more numerous or occurred in pairs after the drug. In 8 of 46 cases the QRS complexes became more narrow after the infusion, possibly as a result of initiation of a higher pacemaker. There was also often a prolongation of the Q-T interval similar to that observed with metabolic alkalosis. The alteration of the T waves recorded after molar sodium lactate is apparently usually secondary to changes in the QRS complexes.

Oral administration of molar sodium lactate has been tried in a few patients. In one, to whom the drug was given orally for 5 days, the heart rate increased moderately and the patient showed a more favorable response to measures employed to relieve congestive heart failure. In cases of hyperkalemia, molar sodium lactate increased the ventricular rate, decreased the width of the QRS complexes, restored normal atrial rhythm, and lowered the serum potassium level. The authors have used this material to restore cardiac activity in 7 patients with Stokes-Adams seizures. During a seizure the sodium lactate may be given by syringe or, in the presence of repeated attacks, it may be given by intravenous drip. Continuous slow infusion may be used to prevent repeated attacks and with an attack the infusion rate may be increased. Molar sodium lactate was used in 12 cases of terminal cardiac arrest, intravenously in 5, and by intracardiac injection in 7 patients. In these cases the heart rate was usually increased from 40 to about 100 beats/min., bizarre QRS complexes became less abnormal, and with continuous artificial respiration, cardiac rhythm could be maintained for relatively long periods, although the blood pressure could not be restored. The critical period following cardiac arrest during which molar sodium lactate must be started to be effective is about 1 or 2 minutes after the onset.

The mechanism of the lactate effect is not clear. The alkalosis and probably the lactate radical are believed to increase the cardiac rhythmicity. There is little evidence that the drug is effective by virtue of sympathetic or parasympathomimetic effects or both.

ROSENBAUM

Clark, R. E.: Failure of Curare to Block the Hypersensitive Carotid Sinus Reflex. Anesthesiology **16:** 771 (Sept), 1955.

The effect of curare was observed in 2 patients with the carotid sinus syndrome who were under anesthesia prior to surgery for carotid sinus denervation. In both patients, the administration of curare intravenously failed to block the cardio-inhibitory response to pressure on the hypersensitive carotid sinus. In 1 patient, curare was completely ineffective in blocking the reflex and in the other it was only partially effective. The slight degree of activity of curare in preventing reactions to carotid sinus pressure is related to its weak ganglionic-blocking effect in the therapeutic dose range. Curare, therefore, is not recommended for the treatment of vagal or depressor manifestations of the carotid sinus syndrome.

SAGALL

Cotten, H. B., Herren, W. S., McAdory, W. C., and Klapper, M. S.: Effects of Rauwolfia serpentina in Patients with Hypertension. Am. J. M. Sc. **230:** 408 (Oct.), 1955.

The effect of several rauwolfia preparations upon the blood pressure and heart rate of 98 hypertensive patients varying in age from 21 to 85 years is presented. About half the patients with hypertension showed a significant hypotensive action with each of the preparations of rauwolfia employed. Bradycardia was observed in an equal number of patients but was apparently unrelated to the blood pressure-lowering influence of the drug. The slowing of the heart rate has several beneficial effects in patients with cardiac hypertrophy except where associated

with aortic insufficiency. This may serve as an additional indication for rauwolfia therapy, distinct from its hypotensive and sedative actions. Starr's formula for cardiac output was employed before and after therapy, disclosing an increase in stroke volume and decrease in output per minute for the majority of patients. There was not a satisfactory correlation between changes in cardiac output and the hypotensive and bradycardiac actions of the drug. The rauwolfia derivatives are the drugs of choice in treatment of mild hypertension, when effective, and have definite advantages over the barbiturate preparations.

SHUMAN

Smith, C. W., Quickel, K. E., Brown, A. E., and Thomas, C. G.: Clinical Experience with a New Combination of Hypotensive Agents. Am. J. M. Sc. **230:** 415 (Oct.), 1955.

A preparation containing rauwolfia, protoveratrine and phenoxybenzamine in fixed proportions was administered to a group of 65 patients with hypertensive disease of varying grades of severity. Extensive clinical and laboratory evaluations were obtained prior to and during the course of treatment. A drop in diastolic pressure of at least 10 mm. occurred in 51 of the patients; 63 per cent were considered to be normotensive at the termination of the study. Thirty-five patients with a good response were given placebo capsules in place of the regular therapy, which resulted in a prompt blood pressure rise. Resumption of therapy controlled the blood pressure in these patients. A statistically significant reduction of the blood urea nitrogen was observed; no other significant laboratory changes were noted. Side effects of nasal stuffiness, fatigue, impotence, palpitation, and weight increase were found and necessitated discontinuance of therapy in 7 instances. Antihistaminics were employed to control nasal congestion and d-amphetamine to control fatigue. The multiphasic approach to the therapy of hypertension is exemplified by this preparation, which exerts both peripheral and central actions, in treatment of a disease with complex and obscure etiologies in most instances.

SHUMAN

Peterson, R. E., Wyngaarden, J. B., Guerra, S. L., Brodie, B. B., and Bunim, J. J.: The Physiological Disposition and Metabolic Fate of Hydrocortisone in Man. J. Clin. Invest. **34:** 1779 (Dec.), 1955.

The metabolism of hydrocortisone has been studied in considerable detail. Following intravenous infusion into normal subjects the half-life in plasma averaged 1.9 hours. Over 90 per cent of the administered hormone was excreted as urinary metabolites in 72 hours. About 4 per cent was excreted in urine as unconjugated substances and less than 1 per cent was excreted unchanged. About 3 per cent appeared in feces; in 1 subject with a biliary catheter 4 per cent of the infused label appeared in the bile.

Patients with liver disease had a slower disappearance of radioactive hydrocortisone from plasma. There was evidence that the defect in hepatic disease may be the reduction of the A ring of hydrocortisone, in which a specific enzyme may be operative.

Compared to other structurally related steroids, the rate of disappearance of hydrocortisone from plasma was slow. The rate was slow also in myxedema, but increased in thyrotoxicosis.

Rapid and complete absorption of tracer amounts of hydrocortisone from the gastrointestinal tract was found, and there was no destruction of the hormone was incubated with gastric juice, bile, or serum.

WAIFE

Sommerness, M. D., Lucero, R. J., Hamlon, J. S., Erickson, J. L., and Matthews, R.: A Controlled Study of Reserpine on Chronically Disturbed Patients. Arch. Neurol. & Psychiat. **74:** 316 (Sept.), 1955.

The effects of suggestion or of a break in ward routine must be measured in evaluating a new drug. A review of the literature failed to reveal an adequately controlled study in the use of reserpine with chronically disturbed long-term mental patients.

Ninety chronically disturbed patients were divided into 3 groups by a random numbers table. One group was given 1 mg. b.i.d. of reserpine orally, the second group was given an apparently identical placebo under identical conditions, and the third group received neither reserpine nor placebo but was otherwise under identical conditions. The patients were kept on this regime for 12 weeks. Patients were rated once every 2 weeks by 2 psychiatric aides using the L-M Fergus Falls Behavior Rating Scale. Blood pressures and weights were recorded every 2 weeks. The results were analyzed statistically.

There was a significant reduction in systolic (10 to 14 mm. Hg) and diastolic (7 to 14 mm. Hg) blood pressures due to reserpine. This drug group also gained weight. There was no appreciable consistent difference in behavior due to reserpine. All the groups (drug-treated, placebo-treated, and non-treated) improved in terms of socially acceptable behavior.

Reserpine tends to bring about a weight gain and a drop in blood pressure. These results are consistent with the findings of other investigators. The drug group did not show any more improvement behaviorally than the other groups receiving nothing or a placebo. This may be because reserpine may not effect chronically disturbed patients or because the dose was too small. Taking the blood pressure every 2 weeks, having the patient weighed regularly, and arousing the interests of the ward personnel seem to account for the favorable behavioral results.

WECHSLER

PHYSIOLOGY

Patterson, G. C., and Whelan, R. F.: Reactive Hyperemia in the Human Forearm. Clin. Sc. **14:** 197 (May), 1955.

Using the venous occlusion plethysmographic method, the authors studied the phenomenon of reactive hyperemia in the forearm produced by short periods of circulatory arrest. They found that in order to obtain quantitative information, it was necessary to measure not only the peak value of hyperemic flow but also the amount of excess blood flowing into the limb during the hyperemic period. Various factors altered the repayment of blood flow "debt," particularly the duration of the arterial occlusion. However, raising the resting level of blood flow either by direct or indirect heating was without effect on the excess blood flow during reactive hyperemia.

The results were considered compatible with the concept of the accumulation of a dilator metabolite during circulatory arrest whose removal, on release of the circulation, was governed by its rate of diffusion into the tissue fluid from the cells in which it was formed.

ABRAMSON

Schocken, K.: The Self-Regulation of the Blood Flow. Exper. Med. & Surg. **13:** 73 (Nov. 1), 1955.

The author defines the term "self-regulated" when applied to a system as indicating a situation in which the system is actuated by the difference between its actual behavior and the desired behavior.

The control system for blood flow consists of the input value, determined by the instantaneous oxygen requirement of the organs, the output value, which is the part of the system driven into correspondence with the input value, and an error-detecting organ in the centers of cardiovascular regulation, which compares the instantaneous values of the input and output flow and produces a signal proportional to any difference between the 2 values. The signal is neural or chemical and controls the output value, so that the magnitude and direction of the change will reduce or abolish the signal produced by the error-detecting organ.

ABRAMSON

Rosensweig, J.: The Effect of the Position of the Arm on the Oxygen Saturation of the Effluent Blood. J. Physiol. **129:** 281 (August), 1955.

The oxygen saturation of the blood taken from the dependent arm vein was found to be higher than that taken from the horizontal arm. If the oxygen saturation of arterial blood and the oxygen consumption of the relevant tissues are assumed to have been unaffected by the change in posture, the raised oxygen saturation of the venous blood indicates that the blood flow was greater when the arm was dependent, though the possibility of a local or transient decrease cannot be excluded. The increase in blood flow may be due to distention of the resistance vessels caused by the hydrostatic effect of lowering the arm. This reported experiment does not support the recent suggestion of Gaskell and Burton, that when a limb is lowered the resulting distention of the veins causes a local reflex vasoconstriction.

AVIADO

Hoshi, T., Kojima, T., Kameyama, S., and Matsuda, K.: On the Influence of Postural Change upon the Cardiac Rate in Man. Tohoku J. Exper. Med. **62:** 221 (Oct.), 1955.

In 16 healthy individuals the effects of alteration of posture on the heart rate were studied. In each case, during the postural change from reclining to sitting and from sitting to standing, the heart rate accelerated immediately. It attained its maximum in 10 to 15 sec., and became stabilized within 60 sec. at a level that was always higher than before. Similar but more pronounced changes were observed in the heart rate on changing the posture from a squat to active standing. The physiologic mechanisms responsible for these changes were discussed. The immediate effect of changing the posture to a more vertical position from reclining appears to be a reduction of venous return to the heart, due to the pooling of blood in dependent parts of the body by gravity. Various circulatory reactions accompanying the postural change were interpreted on this basis and the importance of the cardio-accelerating and vagopressor reflex originating in the venous area was stressed.

BERNSTEIN

RHEUMATIC FEVER

Cotes, J. E.: The Role of Oxygen, Carbon Dioxide and Lactic Acid in the Ventilatory Response to Exercise in Patients with Mitral Stenosis. Clin. Sc. **14:** 317 (No. 2), 1955.

The ventilation and blood lactic acid response to standardized exercise were studied in 20 patients with mitral stenosis. It was found that the exercise and recovery ventilation while breathing air was increased in patients with moderate disability due to mitral stenosis, as compared with normal subjects. When the patients breathed 100 per cent oxygen instead of air during the physical effort, the exercise ventilation was reduced much more than in the control group. From such findings, it was concluded that in the case of the patients with mitral stenosis, an insufficiency of oxygen contributed to the increased exercise ventilation while breathing air.

An exaggerated lactic acid response was also noted in the patients with mitral stenosis. This was considered to be due to the failure of these indi-

viduals to achieve an adequate cardiac output under exercise, and to the sedentary mode of life imposed by their disability. The increase in lactic acid was believed to be responsible in part for the increased ventilation after exercise and for the fatigue that is a prominent feature of the disease.

ABRAMSON

Centeno, P. A.: Myxofibroma of the Left Atrium Simulating Rheumatic Heart Disease. Pediatrics **16:** 489 (Oct.), 1955.

This is a case report on a 3½-year-old boy who manifested dyspnea, and easy fatigability and who had fever, gallop rhythm, and an apical systolic murmur. Heart failure developed and despite the administration of digitalis and ACTH the patient died. It was felt that the patient had rheumatic myocarditis. The sedimentation rate was normal. At necropsy, a myxoma of the left atrium was found. On review, the patient preferred a prone position in his terminal state with his head lower than his trunk. The literature on myxomas of the left atrium is reviewed. The characteristic diagnostic clue, preference for prone position with head lower than trunk, is emphasized.

HARVEY

Broustet, P., Castaing, R., Bricaud, H., and Cottin, D.: Hemodynamic Effects of Acetyl-Digitoxin in Mitral Stenosis. Arch. mal. coeur **48:** 859, 1955.

In 21 cases submitted to cardiac catheterization, 0.10 mg. of acetyl-digitoxin was injected into the pulmonary artery. Increase of the pulmonary ventilation, slight decrease of the heart rate, and decrease of pulmonary capillary and arterial pressures as well as of the right intraventricular pressure were observed in all cases. Increase of the cardiac output appeared in only half the cases. It is suggested that the decrease in the pulmonary arterial resistance observed in these cases may be a direct vascular effect of digitalis.

LEPESCHKIN

ROENTGENOLOGY

Langsam, M., Lewitan, A., Nathanson, L., and Wilensky, D.: Fractionation Technique in Translumbar Aortography and Femoral Arteriography. Arch. Surg. **71:** 120 (July), 1955.

The authors describe a modification of the technic used in obtaining aortograms and arteriograms. First a plain x-ray film of the abdomen is taken with a metallic marker placed 7.5 cm. from the midline and 3.5 cm. from the costal margin. After the film is developed, a site of puncture is chosen that will permit placement of the needles below the level of the renal arteries, i.e., below the lower border of the first lumbar vertebra. The needles are then inserted into the aorta, 5 ml. of sodium acetrizoate (Urokon sodium) is injected, and a scout film is taken. This step is of value in determining whether the needles are placed at the correct level and not in one of the renal arteries. It also is helpful in ascertaining whether the patient will tolerate the remainder of the procedure.

For the second injection 15 ml. of radiopaque medium is used, and then an exposure is made using a regular Bucky film. The latter is large enough to cover the site of injection to the upper 5 cm. of the superficial femoral vessel. The third and final injection is made with 35 ml. of Urokon sodium. Prior to this the patient is positioned on a tunnel that holds 2 14 by 17 inch films. With such an approach the entire limb can be visualized from the hip to the ankle.

ABRAMSON

Gould, D. M., and Daves, M. L.: Roentgenologic Findings in Systemic Lupus Erythematosus. J. Chron. Dis. **2:** 136 (Aug.), 1955.

One hundred cases of systemic lupus erythematosus (S.L.E.) were selected on the basis of certainty of diagnosis and completeness of radiologic coverage.

Those cases selected were proved by any or all of the following criteria: (1) necropsy, (2) biopsy, (3) L.E. cells, (4) typical clinical findings.

Pleural involvement was the most common finding. Seventy-four of 100 cases had some type of pleural reaction during the course of their disease. Fibrinous pleuritis without effusion and in most cases bilateral was found in over one half of the cases. Fifty cases had parenchymatous changes in the lungs thought to be caused directly by S.L.E. The most common type observed was a focal patch of infiltration in the lower lobes. The patch was rarely dense or homogeneous, but instead was loosely reticular or granular and of low contrast. A significant number of linear plaques was also encountered. These plaques formed horizontal bands, indistinguishable from compression atelectasis just above the diaphragm, or radiated from the costophrenic sulcus in a manner radiologically identical to pulmonary infarctions. Cardiac involvement was present in 53 per cent of the patients studied. Most significant was cardiac enlargement with rapid and sometimes pronounced variation in size or configuration. Changes in the joints in spite of clinical evidence of arthritis were minimal and consisted of soft tissue atrophy and osteoporosis. Splenic enlargement was encountered in 34 per cent of patients. Six had evidence of fluid in the abdomen, but there were no patients with massive ascites. Sixteen had evidence of paranasal sinusitis. It is felt that although there is no one specific radiologic feature, S.L.E. may be strongly suspected on the basis of roentgen studies.

MAXWELL

SURGERY AND CARDIOVASCULAR DISEASE

Jordan, P., Jr., and Wible, J.: Spring Valve for Mitral Insufficiency. Preliminary Report. Arch. Surg. **71:** 468 (Sept.), 1955.

A spring valve is described that has been used experimentally in the treatment of mitral insufficiency. It is composed of a metallic frame of Elgiloy, a supersaturated mixture of metals, over which a double layer of nylon has been sewn. The frame consists of a double band of metal with the 2 limbs at approximately 45° from each other. The stem is spot welded at centimeter intervals. Because of the spring of the frame, the valve limbs can be folded and placed within a trocar. When the trocar is removed the valve limbs spring open in the left ventricular chamber and assume a valvular character.

The prosthesis is inserted through the left ventricular wall at right angles to the commissures and below the anterior leaflet. With the examining finger in the left atrium, the spring is liberated from the trocar and adjusted to stop the jet of insufficiency. A nylon covering is sutured to the epicardium.

A study of the results of the use of this prosthesis in dogs has revealed that it appears to move for protracted periods and that it becomes covered by living tissue and firmly fixed to the ventricular wall. This moving prosthesis causes no alterations in the normal clotting mechanism in dogs.

ABRAMSON

Lewis, F. J., Taufic, M., Varco, R. L., and Niazi, S.: The Surgical Anatomy of Atrial Septal Defects: Experiments with Repair Under Direct Vision. Ann. Surg. **142:** 401 (Sept.), 1955.

The authors described the results of 35 operations to repair atrial septal defects using direct vision and hypothermia. The cardiac inflow and outflow were occluded and the right atrium was opened widely. After the defect was repaired, both the right and left heart were filled with saline and the atrium was closed with a clamp. The circulation was resumed before the atrial wound was sutured. The length of inflow occlusion was an average of 4¾ min.

On the basis of their findings at the time of operation, the authors divided the defects of the atrial septum into foramen ovale defects, high defects, continuous defects of both the foramen ovale and the high septum, and low defects.

The conclusions reached were that under direct vision the first 3 types of defects can be satisfactorily repaired by carefully drawing the true margins together with stitches. Attempts to repair low defects are unrewarding and at times catastrophic.

ABRAMSON

Lillehei, C. W., Cohen, M., Warden, H. E., Read, R. C., Aust, J. B., DeWall, R. A., and Varco, R. L.: Direct Vision Intracardiac Surgical Correction of the Tetralogy of Fallot, Pentalogy of Fallot and Pulmonary Atresia Defects. Ann. Surg. **142:** 418 (Sept.), 1955.

The authors presented the results obtained surgically in 10 patients, all seriously ill with various forms of pulmonic stenosis associated with a ventricular septal defect. The defects were corrected during an interval of open cardiotomy ranging from 6 to 21½ min. All the patients were safely maintained during their interval of total by-pass by the cross circulation method. Four of the patients died, while the remaining 6 were asymptomatic postoperatively.

On the basis of their results, the authors concluded that the method of choice for all patients with the tetralogy of Fallot defects in need of surgical treatment is the direct vision intracardiac curative procedure, utilizing controlled cross circulation.

ABRAMSON

Roshe, J., and Morrow, A. G.: The Experimental Production of Graded Aortic Insufficiency. Surg. Gynec. & Obst. **101:** 305 (Sept.), 1955.

The authors describe an aortic leaflet punch for the experimental production of aortic insufficiency. It consists of 2 telescoping stainless-steel tubes, the outer one having a blunt top and the inner one a beveled cutting edge. The latter projects 2 mm. beyond the blunt tip when it is in the extended or cutting position. A polyethylene tube and stopcock are attached to the base of the cutting tube to provide suction.

Before the instrument is inserted into the aorta, total venous inflow is obstructed by temporarily occluding the superior and inferior venae cavae and the azygos vein. A short vertical incision is then made through the wall of the aorta between guide sutures and the aortic leaflet punch is inserted into the vessel. It is guided by palpation until the blunt outer sheath engages the desired cusp of the aortic valve. The stopcock is opened and the inner sheath with its sharp cutting edge is sucked rapidly against the engaged cusp. By gentle rotation, it cuts out a disk of tissue at the base of the cusp.

Using such an apparatus the authors produced lesions in one or both coronary cusps of 46 dogs. Operative mortality was 4 per cent.

ABRAMSON

Swan, H., Virtue, R. W., Blount, S. G., Jr., and Kircher, L. T., Jr.: Hypothermia in Surgery: Analysis of 100 Clinical Cases. Ann. Surg. **142:** 382 (Sept.), 1955.

The authors analyzed the effect of hypothermia on a group of 100 patients undergoing 105 operative procedures, in order to determine the dangers and limitations of this procedure, as well as its potential and actual usefulness in the attainment of operative

objectives. In the series, direct vision intracardiac procedures were performed in 59 instances, closed cardiac operations in 21, and in 20 patients operations were unrelated to heart disease. The hypothermic-operative mortality was 13, while the total mortality was 22.

Among the complications associated with the use of hypothermia were skin burns, thrombophlebitis, gastrointestinal dysfunction, pulmonary complications, and peripheral nerve dysfunction. Twenty-two patients underwent some form of cardiac arrest, an incidence of 1 in 5. The main cause of death was ventricular fibrillation. It was found primarily in patients with diseased hearts who underwent cardiac manipulation.

It was concluded that general hypothermia was of sufficient safety to warrant further clinical use and evaluation, particularly in the case of direct vision intracardiac operations for the correction of congenital lesions by means of a right heart approach.

ABRAMSON

Zech, R. K., Nyhus, L. M., Griffith, C. A., and Harkins, H. N.: Experimental Vascular Grafts, VII. Effects of Growth on Pericardial Autografts. Arch. Surg. **71:** 59 (July), 1955.

The authors studied the effect of growth on pericardial autografts produced in 10 weanling pigs. In each instance, a sheet of pericardium was excised and fashioned into a tube over a Lucite shunt and then sutured into a defect made in the thoracic aorta. Five animals were given nonsupported grafts while the remainder were fitted with a pericardial graft that was then encased in a sheet of fascial tissue removed from the central tendinous portion of the diaphragm.

Seven pigs reached maturity and in all of these the pericardial grafts were found to be patent and functioning well. The 3 nonsupported grafts were thin-walled, and definite aneurysmal dilatations were present in 2 of them. The third was diffusely enlarged and had a thinned area in the lower portion. The supported grafts were similar to the unsupported ones in almost every respect.

Histologically, all grafts showed evidence of degenerative changes that were not as severe as those noted in arterial homografts similarly implanted.

The authors concluded that pericardium as an arterial graft would not seem ideally suitable for implantation in patients.

ABRAMSON

Boyd, D. P.: Carotid Exploration for Hemiplegia Following Mitral Valve Surgery. J. A. M. A. **159:** 112 (Sept. 10), 1955.

The incidence of cerebral embolization during the performance of mitral valve surgery has been estimated at 5 per cent. Such embolization may be due to obstruction of the common carotid artery. This complication may also be caused by obstruction of the internal carotid artery at the bifurcation of the common carotid. It is suggested that the anesthetist should continually observe pulsations in the carotid arteries during the performance of the surgery. In every case where hemiplegia is demonstrated postoperatively, the carotid artery should be explored. All nurses, residents, and others concerned in the postoperative care of these patients should be thoroughly briefed relative to prompt recognition of carotid embolization.

KITCHELL

Shaw, R. S.: Acute Dissecting Aortic Aneurysm. Treatment by Fenestration of the Internal Wall of the Aneurysm. New England J. Med. **253:** 331 (Aug. 25), 1955.

The author describes a man, aged 51 years, who presented a rather typical clinical picture of dissecting aneurysm of the aorta with total obstruction of the aorta above the level of the renal arteries. The aortic obstruction was relieved by evacuation of the clot from the aneurysm and fenestration of the internal aneurysmal wall by excision of a segment 2.0 by 2.5 cm. in size, thereby establishing a double-barreled aorta. The dissection was repaired distally. The immediate postoperative course was complicated by the development of thrombosis of the right popliteal and tibial arteries and subsequent uremia. Death occurred on the ninth postoperative day. However, there was no recurrence of aortic obstruction. The author indicates that aortic obstruction, such as was found in this patient, may be responsible for the frequent systolic hypertension observed in these patients despite their appearance of shock. Furthermore, relief of the obstruction by some surgical procedure should relieve the hypertension and reduce the likelihood of rupture of the weakened proximal aorta.

ROSENBAUM

Ellis, L. B., and Harken, D. E.: Factors Influencing the Late Results of Mitral Valvuloplasty for Mitral Stenosis. Ann. Int. Med. **43:** 133 (July), 1955.

Various factors that affect the late results of mitral valvuloplasty in patients with mitral stenosis were studied in 500 patients. Seventy-eight per cent of the patients surviving operation showed significant and usually persistent improvement over the period of observation, which average 22 months. The best results were in the patients with the greatest degree of stenosis. Less favorable results in the remainder were attributed to the following factors: (1) age over 40, (2) atrial fibrillation, (3) associated aortic valvular disease, (4) associated mitral insufficiency of moderate degree or more, (5) a preoperative valve size of more than 1.0 $cm.^2$, (6) a postoperative valve size of less than 2.5 $cm.^2$ and (7) calcification of the mitral valve. Even in the

less successful categories the over-all results were good in a majority of the patients. Poor results occurred in direct proportion to the number of adverse factors present. The procedure appears to protect substantially against late peripheral embolization, although the incidence of operative emboli is somewhat greater in patients who had previous emboli than in the groups as a whole. Good end results depend on intelligent and careful selection of patients and on the quality of the valvuloplasty.

WENDKOS

Baronofsky, I. D., Borden, C., Smith, R. E., and Sprafka, J. L.: Re-Operation for Mitral Valve Disease. Ann. Surg. **142:** 32 (July), 1955.

The authors describe the findings in 5 patients, during a second mitral valvuloplastic procedure. On the basis of the changes noted and the subsequent postoperative course, they suggest that re-operation after an initial exploratory cardiotomy is perfectly feasible and should be attempted when warranted.

ABRAMSON

Leighninger, D. S., and Beck, C. S.: The Ineffectiveness of Bilateral Sympathectomy on Intercoronary Arterial Communications (Intercoronaries). Ann. Surg. **142:** 274 (Aug.), 1955.

In order to evaluate the effect of sympathectomy on coronary blood flow, the sympathetic chain from above the stellate ganglion to below the level of the eighth to tenth ganglion, was removed bilaterally in a series of mongrel dogs. The Mautz-Gregg backflow method was used to measure blood flow in the circumflex ramus branch of the left coronary artery.

The results revealed no signs of vasomotor influence on the functional intercoronary arterial communications. No evidence was therefore found to support the consideration of sympathectomy as a possible mechanism of benefit in the treatment of coronary artery disease.

ABRAMSON

Nabatoff, R. A., Touroff, A. S. W., and Gross, M.: Four Year Studies Concerning the Fate of Experimental Vena Cava Autografts Used to Bridge Aortic Defects. Surg., Gynec. & Obst. **101:** 20 (July), 1955.

A gross and histologic examination of vena caval grafts substituted for a portion of the abdominal aorta in dogs was performed 3 to 4 years after operation. Up to the time of sacrifice all the animals remained well. The only unusual manifestation was prominent palpable pulsations of the abdomen over the area of the graft. Aortograms revealed obvious dilatation of the graft.

Autopsy findings confirmed the dilatation. In all instances the lumen was patent. Microscopic section demonstrated gradual disappearance of the elastic and muscle tissue coats. All the grafts were surrounded by fibrous tissue. At the end of 4 years, the graft consisted essentially of a thinned-out, fibrous tissue tube lined by endothelium.

It was concluded that if a vein graft is used to bridge a defect in a large artery, it should be provided with some form of external support. Otherwise the high intra-arterial pressure will probably produce marked dilatation of the segment.

ABRAMSON

O'Sullivan, W. D., Roseman, D. M., Lovell, G. R., and Glenn, F.: Tricuspid and Mitral Commissurotomy: A Case Report. Ann. Surg. **142:** 104 (July), 1955.

The authors reported a case of a female patient with multivalvular rheumatic heart disease who was subjected to surgical therapy. First, the mitral stenosis was treated by commissurotomy and a month later tricuspid valvulotomy was performed. The latter operation resulted in a marked increase in tricuspid insufficiency. The patient showed definite clinical improvement, although the objective cardiac signs did not change appreciably.

ABRAMSON

Sakakibara, S.: Surgical Approach to the Correction of Mitral Insufficiency. Ann. Surg. **142:** 196 (Aug.), 1955.

A method is described for the correction of mitral insufficiency. This consists of passing 5 sutures through a segment of great saphenous vein, which is merely a cover for the sutures. The preparation is passed through the left ventricular myocardium over a metal probe in such a manner that it raises the posterior cusp of the mitral valve in order to stop the regurgitation. Each end of the suture is anchored to its respective external heart wall, while the vein covering helps in hemostasis.

The procedure was used on 10 patients with mitral regurgitation. All survived the operation, and 7 patients showed definite improvement in follow-up studies, 7 to 13 months after operation.

ABRAMSON

Coblentz, B., Dubost, C., and Lenégre, J.: Mitral and Tricuspid Stenosis Successfully Treated by Double Commissurotomy. Arch. mal. coeur **48:** 648 (July), 1955.

A case is reported of a 20 year old woman with tight stenosis of both atrioventricular valves. A double commissurotomy was performed successfully, first on the mitral valve, and 2 months later on the tricuspid. By correlation of clinical features of this case with 6 described previously by others, the following criteria diagnostic of such a double lesion are pointed out.

Clinically, there is usually a diastolic rumble extending to the right side of the chest, a progressive dilatation of the right atrium, presystolic pulsation of the jugular veins, and prominent right heart failure. Electrocardiographically the pattern does not differ from that seen in isolated mitral stenosis. At

catheterization, both systolic and diastolic pressures are elevated in the right atrium and pressure gradient to the right ventricle is abnormal. Furthermore, the pulmonary wedge pressure (and left atrial pressure) is lower than expected in mitral stenosis, and a clinical corrollary is the absence of respiratory symptoms.

PICK

Facquet, J., Welti, J. J., Alhomme, P., Lemoine, J. M., and Solignac, P.: Measurements of Left Atrial Pressure by Transbronchial Means in Mitral Disease. Acta cardiol. **10:** 139 (Fasc. 2), 1955.

The technic of transbronchial pressure measurements in the left atrium, as developed by the authors, is described, and typical left atrial pressure curves obtained in normal persons as well as in patients with various types of mitral disease are illustrated and analyzed. The method was performed on 100 individuals without serious accidents.

The most common finding in mitral disease was left atrial hypertension, sometimes very marked. In pure mitral stenosis, during sinus rhythm as well as during atrial fibrillation, there was only slight difference between the lowest and highest value of pressure variations during the cycle. By contrast, in pure or predominant mitral insufficiency, this pressure difference was very prominent and was caused by accentuation of the V wave. The presence of a significant mitral regurgitation was proved by surgery in numerous instances of the latter category.

PICK

Etsten, B., and Proger, S.: Operative Risk in Patients with Coronary Heart Disease. J. A. M. A. **159:** 845 (Oct. 29), 1955.

There were 5,778 surgical patients divided into 3 groups. Group 1 consisted of 517 patients with known coronary disease. Group 2 consisted of 1,107 patients with no history of coronary heart disease but with unequivocally abnormal electrocardiograms. Group 3 consisted of 4,154 patients who had no clinical evidence of heart disease and who had normal electrocardiographic tracings. The postoperative mortality rate for all causes in 517 patients with evidence of coronary heart disease was 2.9 per cent as compared to 2 per cent in 4,154 patients with no clinical evidence of heart disease. The death rate from cardiac causes following surgery was 0.1 per cent in the group of patients with no recognizable heart disease. In 506 patients with chronic coronary heart disease the postoperative mortality was only 0.8 per cent. There were 2 cardiac deaths (18.2 per cent) in a group of 11 patients, who required emergency operations during the course of their acute myocardial infarctions. It is concluded that the operative risk is increased only slightly in patients with chronic coronary heart disease provided proper precautions are taken during and after anesthesia to prevent the impairment of coronary blood flow and of oxygenation.

KITCHELL

van Bogaert, A., and Fannes, E.: The Restrictive Value of Apical Systolic Murmurs in Mitral Commissurotomy. Arch. mal. coeur **48:** 913, 1955.

After cardiac catheterization of 400 cases of mitral stenosis, 25 of whom were operated upon, the conclusion is made that a systolic murmur at or medial to the apex is no contraindication of commissurotomy if the pulmonary capillary pressure at the end of diastole exceeds 20 mm. Hg and tachycardia, atrial fibrillation, or left ventricular failure are not present. If this is the case, the patient will be benefited by the operation, even in the presence of mitral insufficiency. If left ventricular failure is present, the systolic murmur may result from dilatation of the mitral ring, and commissurotomy will not benefit the patient. After extensive commissurotomy a systolic murmur usually appears, but the clinical improvement is considerably greater than after simple digital enlargement of the mitral ostium.

LEPESCHKIN

Baker, H. W., Grismer, J. T., and Wise, R. A.: Risk of Surgery in Patients with Myocardial Infarction. Arch. Surg. **70:** 739 (May), 1955.

Seventy patients with previous myocardial infarcts were subjected to 111 operative procedures.

The operative mortality rate was 3.6 per cent. There was an incidence of 7.2 per cent cardiorespiratory complications. The incidence of deaths and complications was higher in patients with a history of congestive failure and in those with cardiac arrhythmias. There was no apparent relation to angina pectoris, cardiac enlargement, or hypertension. The incidence of complications and deaths was greater in longer operative procedures and in those in which a general or a spinal anesthetic was used rather than a local one.

Five patients were operated upon within 30 days of an acute myocardial infarction; there were no operative complications or deaths. Eleven patients were operated upon within 30 to 90 days of the acute attack; there were 2 complications and no deaths.

While evidence of myocardial infarction may increase the operative risk, it is not a contraindication *per se* to an operation that is urgently needed. Close collaboration between the internist, the surgeon, and the anesthesiologist will contribute toward a successful outcome.

MAXWELL

Pecora, D. V., Brook, R., and Cooper, P.: Pulmonary Infarction Following Interruption of the Pulmonary Artery. J. Thoracic Surg. **29:** 572 (May), 1955.

Usually ligation of the pulmonary artery will not cause infarction, the bronchial artery alone being sufficient to maintain the viability of the lung. During a contemplated right pneumonectomy for epidermoid carcinoma of the right upper lobe, the main pulmonary artery was dissected free and divided. At this stage of the procedure the patient's condition deteriorated, and the operation was therefore terminated. The patient became febrile and died on the tenth postoperative day of a massive infarction of the right lung. Possible mechanisms responsible for the production of the infarction are discussed.

MAXWELL

THROMBOEMBOLIC PHENOMENA

Byrne, J. J.: Phlebitis: A Study of 748 Cases at the Boston City Hospital. New England J. Med. **253:** 579 (Oct. 6), 1955.

The author analyzed a large series of patients with phlebitis who entered a general hospital over a 10-year period. The sex distribution was approximately even. No seasonal variation of the disease could be found. Eighty-three per cent of the cases occurred in patients over the age of 40 years.

Cardiac disease was the most significant predisposing factor in the series (28 per cent), the underlying state responsible for the phlebitis being considered to be venous stasis. In 23 per cent of the cases the condition occurred during the postoperative period, while in 3.7 per cent it was associated with carcinoma. In 6.5 per cent no predisposing disease existed.

With regard to therapy, 347 patients received conservative treatment, and in this group there were 128 deaths (37 per cent). In 369 cases surgical procedures were performed, with 8 deaths (2.1 per cent). In the great majority of cases in the latter series, bilateral femoral vein division was carried out.

The author concluded that fatal pulmonary emboli frequently occur in deep thrombophlebitis as well as in phlebothrombosis. He also felt that bilateral division of the superficial femoral veins should be performed as soon as the diagnosis of phlebitis is made.

ABRAMSON

Tartulier, M., Tourniaire, A., and Guyot, R.: Death Through Pulmonary Embolism: Electrocardiographic Study of Six Clinical and Anatomical Observations. Arch. mal. coeur **48:** 844, 1955.

In all cases massive embolization, involving 80 to 90 per cent of the pulmonary circulation, was present. In 4 cases the syndrome of McGinn and White (S_I, Q_{III}, depression of S-T in I-II, elevation in III and V_1-V_3) was present 5 minutes to 5 hours after embolization, and right bundle-branch block was present in 2 of these. This phase was not seen in 2 cases in which the electrocardiogram was not taken until after clinical death. After clinical death the ventricular rate usually fell during the first 5 min., with A-V and intraventricular conduction disturbances; after the first 5 min. atrial activity disappeared and there was progressive slowing of the idioventricular rhythm with monophasic deformation of the ventricular complexes. This phase persisted up to 65 min. if embolectomy with attempted cardiac reanimation was carried out. Similar changes were observed in 13 dogs after experimental embolism; they are ascribed to anoxia. Ventricular fibrillation appeared late, usually after attempts of cardiac resuscitation, but was never responsible for clinical death.

LEPESCHKIN

Godden, J. O., Hansen, R. E., Hines, E. A., and Christensen, N. A.: Studies of Intermittent Claudication. I. The Effect of Heparin in the Treatment of Intermittent Claudication. Proc. Staff Meet., Mayo Clin. **30:** 437 (Oct.), 1955.

A study of the effect of heparin on intermittent claudication was carried out on 18 patients who were divided into 3 overlapping groups of 12, 12, and 6 patients, respectively. The results of this study showed moderate improvement in claudication-test times in 2 cases. The authors did not consider this improvement to be significant, however. The over-all picture of the response of 6 patients to 16 weeks of treatment with intravenously administered heparin showed very close correlation between the pretreatment and the posttreatment controls. This correlation was the most significant finding of their study.

Many of the studies reported in the literature purporting to show effectiveness of a specific treatment for intermittent claudication have been based on observation by the patient of the distance walked rather than on a standard walking test such as employed in this study. In several reports the evidence of improvement has been based on what amounted to a statement by the patient that he "thought he could walk farther." During this study most of the patients were convinced from their own casual walking experience that they were greatly improved by the treatment, but when tested by the standard walking test none could walk significantly farther than in the period without treatment. This study of the effect of intravenously administered heparin on the symptoms of intermittent claudication carried out over 9 days, 8 weeks, and 16 weeks has not shown a significant increase in the ability to walk among patients thus treated.

SIMON

VASCULAR DISEASES

Berry, R. E. L., and Flotte, C. T.: Peripheral Arteriosclerotic Vascular Disease in Diabetics. Arch. Surg. **71:** 460 (Sept.), 1955.

A comparison was made between the results obtained with sympathectomy in a group of 93

diabetic patients with arteriosclerosis obliterans and another group of 182 nondiabetic subjects with the same disorder. The incidence of symptomatic peripheral vascular ischemia was higher in the nondiabetic under 55 years of age than in diabetic patients of the same age group.

Only 17 diabetic patients were without ulceration or gangrene at the time of hospitalization for peripheral vascular disease. The results from sympathectomy were essentially the same in both diabetic and nondiabetic groups after the onset of gangrene or ulceration. In those cases in which such trophic changes did not exist, the postoperative results in the diabetic patients were not so good as in the nondiabetic group.

It was concluded that up to age 65 the diabetic has an equal, if not slightly better, chance for a good result from sympathectomy. After 65 years only 12 per cent of diabetic patients obtain a good result, as compared with 28 per cent of nondiabetic subjects. The incidence of gangrene in diabetic patients with symptomatic peripheral arterial disease is twice that of the nondiabetic.

ABRAMSON

Keay, A. J., Oliver, M. F., and Boyd, G. S.: Progeria and Atherosclerosis. Arch. Dis. Childhood. **30:** 410 (Oct.) 1955.

The clinical picture of a 3-year-old boy with progeria is presented. Careful endocrinologic studies revealed no obvious abnormalities. Studies on the lipoproteins, however, revealed a pattern quite similar to an adult with atherosclerosis—elevated cholesterol level, elevation of the ratio of total cholesterol to circulating phospholipids, and a high concentration of beta lipoproteins. The relationship between progeria and atherosclerosis is discussed.

HARVEY

Solez, C.: Premature Vascular Degeneration in Diabetes Mellitus: Pathogenesis, and Relation to Aging. J. Am. Geriatrics Soc. **3:** 804 (Oct.), 1955.

Premature arteriosclerosis occurs in both diabetes due to hyperadrenocorticism and in "insulin-deficient" diabetes. The action of glucocorticoids from the adrenal cortex is protein-antianabolic or catabolic. Excess glucocorticoids (as in Cushing's syndrome) cause a wasting of protein tissue throughout the body. The protein tissue of the blood vessel walls is probably involved too. Fatty replacement, calcification, and sclerosis may follow in the wake of degeneration of protein tissue in the vessel walls. Insufficient insulin also causes antianabolic or catabolic derangements affecting the protein tissue of the body. Here again the protein tissue in the blood vessel walls may suffer and be replaced by tissue of a different character. This may give rise prematurely to anatomic changes of senescent degeneration, i.e., arteriosclerosis. Aging itself is a type of protein catabolism or a decreasing protein anabolism; therefore it is not surprising that arteriosclerosis occurs prematurely in the protein catabolic environment of diabetes.

RINZLER

Björk, V. O., and Norhagen, Å.: Thrombosis of the Pulmonary Artery Complicating a Case of Pulmonary Tuberculosis. J. Thoracic Surg. **30:** 108 (July), 1955.

The authors presented a case of thrombosis of the main pulmonary artery associated with pulmonary tuberculosis. The portion of wall containing the process was excised and a continuous suture was applied. The patient made an uneventful recovery. Recurrent thrombosis had not occurred at the time of a 1-year follow-up study.

ABRAMSON

Movius, H. J., II: Resection of Abdominal Arteriosclerotic Aneurysm. Am. J. Surg. **90:** 298 (Aug.), 1955.

The author reported 10 cases of arteriosclerotic abdominal aortic aneurysm treated by resection and replacement with homografts. Four of the grafts used had been stored in a balanced electrolyte solution and the others had been freeze-dried. No patient was refused surgery if the symptoms attributed to the aneurysm were severe. Three deaths occurred, in each instance in relatively poor-risk individuals. The cause of death was ascending thrombosis and shock, uncontrolled sepsis and uremia, and exsanguination from the proximal suture line.

In order to prevent embolization, it was considered advisable to clamp temporarily the aorta above and the iliac arteries below and to inject heparin into the latter to counteract the thrombotic effect of stagnation.

ABRAMSON

Payne, J. H., and Winsor, T.: Management of Acute Popliteal Arterial Occlusion. Am. J. Surg. **90:** 287 (Aug.), 1955.

The authors described several laboratory tests that they considered of value in selecting patients with acute popliteal artery occlusion for partial lumbar sympathectomy. The procedures made it possible to locate accurately the site of arterial obstruction, determine the amount of arterial insufficiency, and estimate the amount of functioning collateral circulation. The study was done on 8 patients with acute popliteal embolism, on all of whom a limited lumbar sympathectomy (L 3) was done as an emergency measure. No further surgery was performed and in each instance the patient was returned to a useful occupation.

The battery of objective tests consisted of the use of the recording oscillometer, the electronic pneumoplethysmograph, and a recording thermistor ther-

mometer. The venous congestion test of the foot was also carried out before and after posterior tibial nerve block.

ABRAMSON

Sharp, A.: Abdominal Aortic Aneurysm: Resection of Bifurcation and Homografting (with hypothermia). M. J. Australia **2:** 125 (July), 1955.

In the case presented, 4 aneurysms were found—1 in the abdominal aorta, 1 in each common iliac artery, and 1 in the right internal iliac artery. Various methods of treatment have been tried. Resection and replacement by a homograft, or by some plastic material, appear to offer the most satisfactory result, provided that the general physical condition of the patient is otherwise reasonably good. With the advent of hypothermia the hazards of this operation have been lessened.

Dry gangrene occurred in the toes of the limb whose artery was occluded for the longer period. This might have been avoided by injecting heparin into the vessel distal to the clamp, but in view of the tendency to bleeding, this drug was withheld. Prolonged interference with the blood supply to the extremities may also be avoided by first by-passing the aneurysm with the graft. After the circulation has been re-established, the isolated aneurysm may then, if necessary, be removed. By decreasing metabolic demands, hypothermia extends the period of safe aortic occlusion. Provided that hypothermia is satisfactorily controlled, the benefits to the patient during the course of a long and extensive operation are many, and not the least appears to be a reduction in postoperative exhaustion.

BERNSTEIN

Bourde, C., Bourdoncle, E., and Jouve, A.: Observations on Arterio-Venous Fistulas of the Limbs. Tentative Classification. Arch. mal. coeur **48:** 775, 1955.

This study of 28 cases shows that the best method for the diagnosis of arteriovenous fistulas is serial arteriography and determination of venous oxygen saturation; venography after venous compression may give equally good visualization in certain cases. In group 1 (congenital hypertrophic hemangiectasis of Parkes-Weber), a continuous murmur with systolic accentuation is present in addition to the triad of nevus or angioma, varices, and osseous hypertrophy. In group 2 (Klippel-Trenaunay syndrome) the triad is present without the murmur. In this case, congenital hypoplasia or obliteration of deep veins is directly responsible for osseous hypertrophy through venous stasis, and probably is also responsible for dilatation of pre-existing arteriovenous anastomoses. The glomic character of these anastomoses precludes the appearance of an audible murmur, which is present in group 1, where the fistula is direct and the prognosis is worse. Group 3 includes fistulas of traumatic origin, while group 4 contains fistulas due to simple varices or phlebitis. In group 5 the shunt appears during the course of an arteritis. There may be transitions between the different groups.

LEPESCHKIN

Harpuder, K.: Rehabilitation of the Patient with Arterial Disease of the Limbs. Geriatrics **10:** 451 (Oct.), 1955.

Rehabilitation of the patient with peripheral arterial disease (Raynaud's syndrome, thromboangiitis obliterans, and obstructive arteriosclerosis) may include psychiatric care, physical care, training of the amputee, and adjustment of the patient and his family to a new and restricted life. Rehabilitation differs in each of the 3 diseases because the damage produced by the disease is different and because the personality of the patient varies in each. Raynaud's syndrome, which produces spasm of the digital arteries upon exposure to cold and upon emotional stimuli, involves younger people and predominantly women. Buerger's disease occurs almost without exception in smokers. It appears in young men of every race and skin pigment. It is rare in women smokers. Obstructive arteriosclerosis appears in the higher age groups and in young diabetics whose disease is of long standing. There is only slight male preponderance.

RINZLER

OTHER SUBJECTS

Harned, H. S.: Cardiac Catheterization in Diagnosis. Connecticut Med. J. **19:** 745 (Sept.), 1955.

The technic of cardiac catheterization as it has been applied to cardiac diagnosis of children and adults is discussed, and interpretation of the data obtained by cardiac catheterization is reviewed. The dangers of the procedure and difficulties in interpretation of results are outlined and would indicate the necessity of extensive training of the members of the cardiac diagnostic team. The changing indications for the procedure in cardiac diagnosis are enumerated in relation to the experience of a cardiac surgical team at a large general hospital.

BERNSTEIN

Tourniaire, A., Fournie, G., Blum, J., and Semet, J.: The Heart in Muscular Dystrophy. Arch. mal. coeur **48:** 738, 1955.

Of 30 published cases of clinical and anatomic involvement of the heart in muscular dystrophy, only 11 showed no other possible cause of the cardiac changes; in 7 cases endocardial fibrosis and aortic hypoplasia were also present. Of 157 published cases, electrocardiograms were definitely abnormal in 63; of these, only 13 could not have been due to other causes. In none of the published cases was unexplained cardiac insufficiency present in a person under 40. In a personal case (a 39-year-old man),

congestive heart failure with considerable radiologic enlargement of the heart was present; the electrocardiogram showed atrial fibrillation with, at times, right and, at times, left bundle-branch-block pattern, sometimes appearing in the form of paroxysmal tachycardia followed by long pauses. At autopsy, the heart was of normal size and weight but showed constrictions, bifurcations, and fragmentations of the myocardial fibers, which often ended in sclerosed sections; myolysis, irregular form of the nuclei, and interstitial fibrosis were often seen. This case, in which the clinical, electrocardiographic, and anatomic changes could not be attributed to any other cause except muscular dystrophy, is an important argument in favor of the participation of the myocardium in the process of muscular dystrophy.

LEPESCHKIN

Silverman, J. J., and Bernstein, A.: The Cardiologis Looks at the Skin. J. A. M. A. **158:** 821 (July 9) 1955.

An extraordinary amount of clinical information is available to the cardiologist from an ordinary examination of the skin. Emotional influences, congenital disorders, bacterial endocarditis, endocrine disorders, metabolic disorders, liver disorders, uremia, nutritional deficiencies, collagen diseases, rheumatic fever, shoulder-hand syndrome, beryllosis and sarcoidosis, infections, herpes zoster, toxic and drug sensitivity reactions, trauma, dissecting aneurysm of the aorta, peripheral vascular disorders, sickle-cell anemia, heart failure and shock give various skin changes that may be recognized by careful examination. Physical examination still plays a dominant part in the study and management of patients suffering from cardiac disorders. There are times when the eyes may yield more information than the stethoscope or the electrocardiogram, and, to be complete, a cardiovascular survey should always include such careful study.

KITCHELL

Covino, B. G., and Hegnauer, A. H.: Ventricular Excitability Cycle: Its Modification by pH and Hypothermia. Am. J. Physiol. **181:** 553 (June), 1955.

Hypothermia is usually associated with acidosis, which depends upon respiratory factors. If blood pH is maintained in a normal range during the bout of hypothermia, there is no lowering of ventricular and minor-dip thresholds. It is the depression of these thresholds that contributes to the ventricular fibrillation observed during hypothermia.

Temperature affects the major-dip portion of the excitability-recovery curve and lowers the threshold slightly. The acid shift lowers diastolic and minor-dip thresholds, but changes the major-dip threshold only slightly. Changes in acidity were observed to affect ventricular excitability at normal temperatures. Also, if acidity were neutralized at normal temperatures, the increased excitability was reversed. During hypothermia acidosis comes on slowly. In this case, reversal of pH does not revert thresholds to normal. Injury current, which is present, is observed to persist, and ventricular fibrillation is just as likely to take place. Rewarming may eliminate the injury current.

OPPENHEIMER

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

All physicians planning to attend the American Heart Association's 32nd Annual Meeting and 29th annual Scientific Sessions in Cincinnati, October 26 through November 2, are urged to register in advance. Registration forms are now available from the Association.

The Scientific Sessions will get underway on Friday evening, October 26, with a special program on instrumentation. They will continue through Monday, October 29. Tuesday and Wednesday, October 30 and 31, will be donated to meetings of the American Heart Association Assembly, with the election of new officers and the installation of Edgar B. Allen, M.D., Rochester, Minn., as President scheduled to take place on Wednesday morning. On Monday, Wednesday, Thursday and Friday there will be meetings of Heart Association staff personnel.

The following is a tentative program of the Scientific Sessions:

Friday evening, October 26: Instrumentation, Electrocardiography, Ballistocardiography, and Vectorcardiography. Netherland Hilton Hotel.

Saturday, October 27: Morning—General Sessions; Lewis A. Conner Memorial Lecture; Annual Meeting of Scientific Council. The Conner lecture will be given on the subject of *Functional Pathology of the Pulmonary Vascular Tree in Congenital Cardiac Disease*, by Jesse E. Edwards, M.D. *Afternoon*—Panel discussion, "Selection and Management of Patients for Cardiac Surgery;" Special Sessions of Section on Clinical Cardiology; Section on Cardiovascular Surgery; and Section on Circulation and Basic Science (jointly).

Sunday, October 28: Morning—General Session; George E. Brown Memorial Lecture. The Brown Lecture will be delivered by Hugh Montgomery, M.D., on the subject of *Oxygen Tension of Tissues in Vivo*. *Afternoon*—Panel discussion on "The Management of Refractory Congestive Heart Failure;" Special Sessions of the Sections on Basic Science and Circulation (jointly); of the Section on Clinical Cardiology; of the Council for High Blood Pressure Research; and program discussions of the Council on Community Service and Education. *Evening*—Annual Dinner of the American Heart Association, Netherland Hilton Hotel.

Monday, October 29: Morning—General Session; Panel discussion on "Cardiac Rehabilitation." *Afternoon*—Panel discussion on "The Recognition and Management of Cardiac Arrhythmias;" Special Sessions of Sections on Circulation and Basic Science (jointly); of Section on Clinical Cardiology; and of the Council on Rheumatic Fever and Congenital Heart Disease.

A more complete final program will be published in the October issue of *Circulation*. Abstracts of the scientific papers will be published in the November number of the journal. In the above schedule, all events are to be conducted at the Music Hall unless otherwise stated. The Netherland Hilton Hotel, formerly known as the Netherland Plaza, will serve as AHA headquarters throughout the Annual Meeting and Scientific Sessions.

The registration forms available from the Association also provide information on hotel accomodations and space for securing reservations. Forms may be obtained on request from the AHA, 44 East 23 Street, New York 10, N. Y.

AHA FELLOWSHIP APPLICATIONS DUE BY SEPTEMBER 15

September 15 is the deadline for submitting applications for research fellowships and established investigatorships to be supported by the Association during the fiscal year beginning July 1, 1957. Applications for grants-in-aid during the same period must be received by the Association no later than November 1, 1956. All applications must be made on forms avail-

able from the Association. Forms issued in previous years should not be used.

The following are descriptions of the types of awards involved:

Established investigatorships: Awarded for periods of up to 5 years, subject to annual review, to scientists of proven ability who have developed their research careers to the point where they are independent investigators. Initial stipend is $6,000 and annual increments are $500.

Research Fellowships: To individuals with M.D. or Ph.D. degrees for periods of 1 to 2 years to enable recipients to obtain further research experience under supervision of senior investigators. Initial stipends range from $3,500 to $5,000 with the exact amount determined largely by the number of dependents. There is a modest increase after 1 year.

Grants-in-aid: To experienced investigators to provide support for specific research projects. They are usually made for periods of 1 to 3 years.

Further information and application forms may be obtained from the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

CEREBRAL VASCULAR CONFERENCE PLANNED FOR JANUARY

A Second Conference on Cerebral Vascular Diseases to be held in Princeton, N.J., under the sponsorship of the American Heart Association has been announced by Irving S. Wright, M.D., New York, the Conference Chairman. Attendance at this conference, which is to start on Wednesday, January 16 and to continue into Friday afternoon, January 18, will be by invitation only.

The conference will follow the pattern set by its predecessor held in 1954. It will be conducted as a series of round table discussions involving approximately 40 participants. All discussions will be transcribed, edited and published as Transactions. These will be made available to the medical profession.

Among the disciplines to be represented at the conference will be pathology, brain chemistry, physiology, blood coagulation studies, neurology, neurosurgery, psychiatry, electroencephalography and studies in the fields of hypertension, atherosclerosis and rehabilitation.

Grants from the National Heart Institute and the Albert and Mary Lasker Foundation will help to underwrite the expenses of the conference.

WASHINGTON STATE SPONSORS CARDIAC SYMPOSIUM, SEPT. 28–29

The Eighth Annual Symposium on Heart Disease to be conducted jointly by the Washington State Heart Association and the Washington State Department of Health will be held at the University of Washington Medical School Auditorium in Seattle, September 28 and 29. This year the symposium will be devoted to peripheral vascular disease and congenital heart disease.

Among those who will present papers will be Frederick Bentley, M.D., Portland, Ore.; S. Gilbert Blount, Jr., M.D., Denver; Denton A. Cooley, M.D., Houston; C. Walton Lillehei, M.D., Minneapolis; and J. Lowell Orbison, M.D., Rochester, N. Y. The speakers will also conduct panel discussions and answer questions from the audience.

The symposium will be credited by the Academy of General Practice on an hour-for-hour attendance basis. Additional information may be obtained from the Washington State Heart Association, 3114 Arcade Building, Seattle, Wash.

WESTERN CARDIAC CONFERENCE SCHEDULED IN DENVER. NOV. 5–10

Clinical electrocardiography and recent advances in cardiovascular medicine will be discussed at the Fifth Western Cardiac Conference to be held at the Cosmopolitan Hotel and at the Veterans Administration Hospital in Denver, November 5–10.

The electrocardiograph studies will be on the agenda for the first 3 days while in the last 3 days, the conference will turn its attention to reports on recent progress. Sponsoring the conference will be the Colorado Heart Association, the University of Colorado Medical Center, the Fitzsimons Army Hospital, the Veterans Administration Hospital and the Colorado State Department of Public Health.

Additional information may be obtained from Elizabeth E. Kaho, Administrative Assistant, Colorado Heart Association, 901 East 17th Avenue, Denver 18, Colo.

MEETINGS CALENDER

September 17–20: American Hospital Association, Chicago. Edwin L. Crosby, 18 E. Division St., Chicago 10, Ill.

September 25–28: American Roentgen Ray Society, Los Angeles. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa.

September 28–29: Eighth Annual Symposium on Heart Disease, Seattle. Washington State Heart Association, 3114 Arcade Building, Seattle 1, Wash.

October 6–13: College of American Pathologists, Chicago. Arthur H. Dearing, 203 N. Wabash Ave., Chicago 1, Ill.

October 7–12: American Society of Clinical Pathologists, Chicago. C. G. Culbertson, 1040 W. Michigan St., Indianapolis 6, Ind.

October 8–12: American Society of Anesthesiologists, Kansas City, Mo. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago 1, Ill.

October 8–12: American College of Surgeons, San Francisco. Michael L. Mason, 40 E. Erie St., Chicago 11, Ill.

October 26–31: Scientific Sessions of the American Heart Association, Cincinnati. American Heart Association, 44 E. 23rd St., New York 10, N.Y.

November 5–10: Fifth Western Cardiac Conference, Denver. Miss Elizabeth E. Kaho, Colorado Heart Association, 901 E. 17th Ave., Denver 18, Colo.

November 7–9: American Academy of Obstetrics and Gynecology, Chicago. C. Paul Hodgkinson, 116 S. Michigan Blvd., Chicago 3, Ill.

November 8–10: Gerontological Society, Chicago. Nathan W. Schock, Baltimore City Hospitals, Baltimore 24, Md.

November 11–12: American Society for the Study of Arteriosclerosis, Palmer House, Chicago. O. J. Pollak, M.D., P.O. Box 228, Dover, Del.

November 12–14: Association of Military Surgeons of U.S., Washington, D.C. R. E. Bitner, 1726 Eye St., N.W., Washington, D.C.

November 12–14: Association of American Medical Colleges, Colorado Springs. Dean F. Smiley, 185 N. Wabash Ave., Chicago, Ill.

November 12–16: American Public Health Association, Atlantic City, N.J. Dr. Reginald M. Atwater, 1790 Broadway, New York 19, N.Y.

November 17–19: American Academy for Cerebral Palsy, Chicago. Robert A. Knight, 869 Madison Ave., Memphis 3, Tenn.

November 27–30: American Medical Association Clinical Meeting, Seattle. Dr. George F. Lull, 535 N. Dearborn St., Chicago 10, Ill.

December 2–7: Radiological Society of North America, Chicago. D. S. Childs, 713 E. Genessee St., Syracuse 2, N.Y.

ABROAD

September 19–23: International Congress of Internal Medicine, Madrid. Dr. Carlos Jimenez Díaz, Facultad de Medicine, Madrid, Spain.

September 21–23: Extraordinary General Assembly of the Medical Women's International Association, Burgenstock, Lucerne. Dr. Janet Aitkin, 30a Acacia Road, London, N.W. 8.

September 28–29: International Professional Union of Gynecologists and Obstetricians, Madrid, Spain. Dr. Jacques Courtois, St. Germain-en-Laye, Seine-et-Oise, France.

October 9–15: World Medical Association, Havana. Dr. L. H. Bauer, 345 E. 46th St., New York 17, N.Y.

November 11–17: Inter-American Congress of Cardiology, Havana, Cuba. Dr. Ignacio Chavez, Calzada de la Piedad Num. 300, Mexico, D.F. Mexico.

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM AND PROCEEDINGS OF THE TENTH ANNUAL MEETING AT THE PALMER HOUSE, CHICAGO, ILL., NOVEMBER 11 AND 12, 1956

(All papers except the Addresses will be limited to 10 minutes for presentation plus 5 minutes for discussion.)

SUNDAY MORNING NOVEMBER 11, 1956

A. C. Corcoran, Presiding

8:00 Registration

9:00

1. Blood Coagulability: Effects of Meals and Differences between Populations

Ancel Keys and Ratko Buzina. From the Laboratory of Physiological Hygiene of the University of Minnesota, Minneapolis, Minn.

Whole blood coagulation times (WBCT) in siliconized tubes, as well as other measures of coagulability, were systematically standardized as to methods, reproducibility, etc. Different values of WBCT under basal conditions were found to be characteristic of different "normal" individuals and these differences were not regularly altered by a few weeks of changing the fat level of the diet. Rigidly controlled tests, however, showed that WBCT, and to a lesser extent some other measures of coagulability, tends to be shortened after a fatty meal, the largest effect appearing at 3 to 5 hours and being little correlated with the degree of lipemia as indicated by plasma turbidity. Measurements of WBCT in several hundred fasting "normal" Minnesota men failed to show any correlation with age but significant differences were found between different occupational groups. The greatest frequency of short WBCT was observed in business and professional men and the least among physically active railroad switchmen. The relationships between these findings and other characteristics of the men will be discussed with a view to the possible relevance of these findings to problems of the frequency of intravascular thrombosis in different populations.

9:10

2. Plasma Lipids and Coagulation of Blood

Ezra Sohar, Martin C. Rosenthal and David Adlersberg. From the Departments of Medicine, Hematology and Chemistry of the Mount Sinai Hospital, New York, N. Y.

Coagulation studies were performed on 7 controls, 6 persons with idiopathic hyperlipemia and 5 persons with idiopathic hypercholesteremia, before and after a standard fat meal. In none of the subjects was there an alteration of the standard clotting time, 3-tube silicone clotting time, standard prothrombin time, serum prothrombin activity, thrombin generation and thromboplastin generation.

There was, however, depending upon their triglyceride content, a distinct difference in the behavior of various plasmas to the action of "incomplete" thromboplastin (Stypven). Stypven prothrombin time showed definite shortening in 4 of 5 healthy controls following fat ingestion. In the 1 subject who showed no shortening, the expected rise in serum triglycerides (neutral fat) failed to occur. In the persons with idiopathic hyperlipemia Stypven prothrombin times were abnormally shortened prior to fat ingestion and were only slightly influenced following the fat meal. In the persons with idiopathic hypercholesteremia the Stypven prothrombin time was as in the controls. Chemical and electrophoretic studies revealed shortening of the Stypven prothrombin time to be correlated with an increase in serum triglycerides. Centrifugation of hyperlipemic

plasma into 2 fractions, fat rich and fat poor, also revealed a correlation between fat content and shortening of the Stypven prothrombin time. No change in erythrocytic fragility, osmotic or mechanical, was revealed following ingestion of food. Intact platelets and, even more so, disrupted platelets, exerted an effect similar to that of triglycerides, in that they shortened the Stypven prothrombin time.

The presence in the plasma of a thromboplastin potentiator (triglycerides) either postprandially in the normal or, perhaps more important, constantly in the hyperlipemic subject, may result in increased coagulability and thrombosis when thromboplastic material is liberated into the blood stream.

9:20

3. A New Method for the Control of the Oral Anticoagulants

W. Ford Connell and G. A. Mayer. From the Department of Medicine, Faculty of Medicine, Queen's University, Kingston, Ontario, Canada.

The Quick one-stage prothrombin test, or some modification thereof, is commonly considered essential to the management of oral anticoagulant therapy. The authors report on their experience with an entirely different method of control. This consists of a highly reproducible standardized clotting time (SCT) performed on unmodified venous blood. It has been used, during the past 2½ years for the control of such therapy in 245 cardiovascular patients, for a total of 12,350 patient-days. The Quick one-stage prothrombin test (PTR) was carried out, for comparison, in the first 175 cases. The following drugs were used in the course of this study: bishydroxycoumarin, ethyl biscoumacetate, acenocoumarin and phenindione.

All drugs used produced a significant and consistent prolongation of the SCT; the time required to produce such prolongation averaged 4 days or longer for all four drugs studied.

No significant correlation was found between the 2 tests. Adequate SCT prolongation was found at widely varying levels of PTR.

We experienced no difficulty in maintaining the SCT within our therapeutic range in 80 per cent of the total treatment days. When the SCT was in this range, we saw no hemorrhagic accidents or thromboembolic complications. The PTR gave no reliable warning of the imminence of such accidents and complications.

Our data demonstrate that the SCT as used by us is a more reliable guide to oral anticoagulant control than is the Quick 1-stage prothrombin test. In the past 8 months, indeed, this test has been used alone, in 70 patients, for the control of oral anticoagulant therapy, for a total period of 1177 treatment days, with excellent clinical results.

9:30 Discussion

9:45

4. Studies on the Mucopolysaccharides of Human Arterial Tissue*

J. E. Kirk and M. Dyrbye. From the Division of Gerontology of Washington University, St. Louis, Mo.

Determinations were made of the concentrations of hexosamine and acid-hydrolyzable sulfate in samples of the human aorta and pulmonary artery obtained fresh at autopsy. The age of the individuals from whom the samples were derived ranged between 1 month and 89 years. The hexosamine analyses were performed by Boas' modification of Elson and Morgan's method. The average hexosamine concentration found in the aorta (N = 113) was 0.30 per cent (calculated on the basis of wet tissue weight), and in the pulmonary artery (N = 85) 0.27 per cent. For determination of acid-hydrolyzable sulfate, homogenates of the arterial tissue were heated at 118 C. with hydrochloric acid in closed ampoules for 15 hours; the sulfate present in the hydrolysates was precipitated with benzidine and measured by a spectrophotometric method devised by the authors. The average sulfate concentration found in the aorta (N = 101) was 0.075 per cent (calculated on the basis of wet tissue weight), and in the pulmonary artery (N = 68) 0.070 per cent.

No significant change with age was observed in the hexosamine and sulfate concentrations of the aortic tissue. The hexosamine content of the pulmonary artery likewise remained unchanged with age, whereas higher tissue sulfate values were recorded for 50 to 79 year old individuals as compared with younger subjects.

Isolation of mucopolysaccharides from aortic tissue was effected by a modification of Pearce and Watson's procedure. Electrophoresis of the isolated material revealed the presence of 2 fractions which stained metachromatically with toluidine blue. One of these fractions showed a mobility similar to that of chondroitin sulfate prepared from cartilage; the mobility of the other fraction was distinctly slower.

9:55

5. Distribution of Metachromasia in Aortas Fixed at Blood Pressure

C. H. Lupton, Jr. and J. F. A. McManus. From the Department of Pathology of the University of Alabama Medical Center, Birmingham, Ala.

The technique of Crawford and Levene for fixing aortas at the systolic pressure present during the

* The investigation was supported by a grant (PHS-891) from the National Heart Institute of the National Institutes of Health, Public Health Service.

life of the individual has been used by Morgan and McManus to determine the proper position of atheromatous plaques during life. As the British authors have described, the atheromatous plaques fit smoothly into the vessels and do not ordinarily project into the lumen of the aorta.

The present report describes the distribution of metachromasia and ground substance materials coloring with carbohydrate stains (toluidine blue, PAS, alcian blue) in materials fixed at atmospheric and at systolic blood pressure. Larger collections or pools of carbohydrate-staining material were found in the aortas which had been fixed at atmospheric pressure. These observations re-emphasize the necessity for physiological considerations during the study of vascular disease and suggest the necessity for restudy of the relationships of ground substance to atherosclerosis.

10:05 Discussion

10:15

6. The Role of Acid Mucopolysaccharides in the Development of Atherosclerosis in the Rabbit

Chun-I Wang, Lotte Strauss and David Adlersberg. From the Departments of Medicine and Pathology, Mount Sinai Hospital, New York, N. Y.

In a group of 35 male rabbits fed 1 Gm. of cholesterol daily for time periods from 2 weeks to 10 months, varying degrees of atherosclerotic lesions were observed in the large and small arteries. The relation of acid mucopolysaccharides of the ground substance to the lipid deposition in these lesions was studied using the colloidal iron technic (modification by Rinehart and Abul-Haj).

Histologically, the earliest alteration of the arterial wall, invisible to the naked eye, consisted essentially of an accumulation of acid mucopolysaccharide in the intima. The area of increased deposition of acid mucopolysaccharides was usually sharply delineated by the internal elastic membrane. In small arteries such as the coronary arteries and the arterioles of the spleen or the pancreas the swelling of intimal cells was accompanied by an intensified intracellular colloidal iron reaction. With the deposition of lipids and appearance of foam cells, the colloidal iron-positive material could be seen only faintly as a delicate network in the foam cells. In advanced atherosclerotic lesions, intra and extracellular accumulation of lipids dominated the picture. It appeared that accumulation of acid mucopolysaccharides furnished a "matrix" which probably preceded lipid deposition and was closely related to the process of experimental atherosclerosis in the rabbit.

10:25

7. Effects of Sulfated Polysaccharides on Pre-established Atherosclerosis in the Presence of Continued Cholesterol Feeding

P. Constantinides and P. Saunders. From the Department of Anatomy of the University of British Columbia, Vancouver, B. C., Canada.

Heparin and sulfated alginic acid (SAA) treatment was instituted in rabbits some time after the development of cholesterol atherosclerosis and was carried on in the presence of continued high cholesterol intake.

Under the conditions of this experiment, SAA displayed considerably greater antilipemic activity than heparin. SAA abolished the lactescence of the serum and reduced the hypercholesteremia whereas heparin reduced the lactescence and had no significant effect on the hypercholesteremia.

Both heparin and SAA arrested the expansion of the pre-established atheroma area in the aorta and visceral arteries but only SAA arrested the further deposition of cholesterol in the aortic lesions.

Qualitative changes suggestive of incipient regression appeared in several aortic plaques of heparin as well as SAA treated animals. These changes consisted of central shrinkage, histological lipid depletion and calcification of the underlying media.

Both heparin and SAA inhibited xanthoma formation in the interstitial stroma of the kidney, and protected the parenchyma of this organ from destruction secondary to atherosclerosis.

Heparin suppressed whereas SAA increased the appearance of foam cells in the spleen, the mesenteric lymph nodes and the renal glomeruli.

10:35 Discussion

10:45

8. The Origin of Blood Cholesterol

David M. Tennent, Mary Zanetti, David I. Atkinson, Gunther Kuron and David F. Opdyke. From the Merck Institute for Therapeutic Research, Rahway, N. J.

Several investigators have been occupied with the problem of determining the source of blood cholesterol. This is an important step in understanding lipid transport and metabolism. It would seem that the liver is probably the principal source, but clear-cut evidence for this has been hard to obtain. It is well known that liver slices synthesize cholesterol in vitro, but it is also reported that perfused livers do not introduce cholesterol into the perfusate unless the livers are damaged. It has been found that hepatectomized animals do not produce blood cholesterol, but this might be because the source of substances involved in cholesterol trans-

port rather than the source of cholesterol itself has been removed. Better evidence is that after injection of tagged acetate, liver was the only tissue studied in which the cholesterol had greater specific activity than did the plasma cholesterol.

We have studied synthesis of cholesterol from acetate by dog heart-lung-liver preparations, set up with minimal disturbance to the liver, using heart-lung preparations as controls. The heart-lung-liver preparations introduced cholesterol into the blood stream, but the heart-lung preparations did not. The specific activity of liver cholesterol was greater than that of blood cholesterol, which in turn was greater than that of heart or lung cholesterol, and thus the blood cholesterol must have come from the liver.

We have shown in an isolated system that the intact liver synthesizes cholesterol and introduces it directly into the blood stream.

10:55 Discussion

11:00

9. A Method for Studying Aortal Lipid Metabolism In Vitro

N. T. Werthessen, J. W. Hahn and M. A. Nyman. From the Southwest Foundation for Research and Education, San Antonio, Tex.

The previously described technic of maintaining the excised aorta in vitro is employed. Four perfusions are now run simultaneously, using aliquots from a common pool of blood. The first 2 aliquots of the blood, 1 with and 1 without the addition of the agent under study, are perfused through glass cannulae as substitutes for aortas. The second 2 aliquots, 1 with and 1 without the additive, are perfused through composite aortas, the cephalad portion of 1 aorta being tied to the caudal portion of the other and vice versa. This permits examination of the system with reference to agents affecting lipid synthesis, conversion, and the movement of lipids between aorta and blood.

The experiments are run for 24 hours at hypertensive pressures. Acetate is added to each perfusion and aliquots are taken periodically. At the end of the run, the perfusates and the aortas are extracted with Delsal's reagent to give the total lipids. These are analyzed with respect to isotope incorporation, cholesterol, and phospholipid level. One portion of the extract is chromatographed through a silica gel column. The chromatographic fractions are counted with a liquid scintillation counter. The fractions are grouped according to their chromatographic behavior and the total count per minute for each group determined.

By this means, the relative rates of synthesis of the lipids by the blood, by the aorta, and by the blood and the aorta as modified by the agents are obtained. Since the same blood and aorta (a composite) is used throughout the system, a complete study of distribution of newly synthesized lipids is feasible. The chromatographic technic permits separation of the lipids into several classes which can be examined separately. The effects of agents such as p-aminobenzoic acid, estrone, testosterone, Seifter's lipotrophic extract, etc., on the system will be reported. In general, it can be stated that the agents studied affect the lipid metabolism both as to the extent of synthesis of the various groups in the lipid profile and their movements in and out of the aorta.

11:10 Discussion

11:15

10. The Phospholipid Composition of Human Aortic Intima

Herbert J. Kayden and J. Murray Steele. From the Research Service, Third (New York University) Medical Division, Goldwater Memorial Hospital, Welfare Island, New York, N. Y.

The separation of human sera into α- and β-lipoprotein by electrophoresis, using starch as a supporting medium permitted chemical analysis of the cholesterol, total phospholipid, lecithin and sphingomyelin in these fractions. Lecithin was found to be equally distributed between α and β fractions but ¾ of the sphingomyelin was present in the β fraction. The range of the lecithin: sphingomyelin ratios of whole serum is from 3.7 to 9.0 (mean 6.2), of α-lipoprotein from 4.0 to 18.5 (mean 9.8), and of β-lipoprotein from 1.8 to 5.6 (mean 3.2). Direct organic solvent extraction of the arterial wall (intima) in this laboratory yielded a lecithin: sphingomyelin ratio of about 5 in adolescence which falls to 1 and even lower as aging and atherosclerosis occur.

With the possibility that some of the lipid in the aorta might be present as a lipoprotein complex, homogenates of the aortic intima were extracted with saline and analyzed. It appeared that anywhere from 25–85 per cent of the total lipid material can be found in the "saline soluble" fraction. When this saline extract is subjected to electrophoresis, about half of the material, as estimated by lipid analysis, migrates to the same position as the β-lipoprotein fraction of normal sera. The remainder stays at the origin. In a normal aortic wall, this mobile β fraction yielded a lecithin:sphingomyelin ratio of 3.6. The average value for this ratio in the β fraction of serum was 3.2. In older diseased vessels, the ratio of lecithin to sphingomyelin has been found to be from 0.7–1.06.

These data suggest that a considerable proportion of the lipid of the aortic intima of humans is associated with a protein moiety and that this complex has some characteristics of the β-lipo-

proteins of human serum. The phospholipid composition of this component in normal youthful aortic wall is similar to that of normal human sera β-lioproteins but the change which occurs in this fraction along with aging and the development of atherosclerosis strongly suggests that simple infiltration by β-lioproteins is only a partial explanation of the lipid content of aortic wall.

11:25 Discussion

11:30

11. Physical Factors in the Genesis and Progression of Stenotic Lesions

Simon Rodbard. From the University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y.

Endovascular cushions or plaques can result from the action of physical forces alone. Following studies which showed that deviation of flow lines through arteries in animals induced intimal proliferations and led to coarctation and stenotic lesions, the effect of physical factors on the structure of plastic channels was investigated. In 300 experiments, flow induced the development of cushions in channels lined with deformable silicone. This occurred first at convergences, angulations and arcs of the stream bed. Once formed, such plaques increased in size and a similar plaque was induced on the opposite wall of the channel; ultimately the lumen of the stream became stenosed and flow was inhibited. The presence of a plaque formation at one site led to the induction of new plaques at regular intervals downstream. Tags of material on the downstream end of the plaques formed excrescences whose pedicles extended and thinned until the polyp was swept downstream as an embolus. At sites of pressure drop the lining sometimes was "lifted" from the outer wall, producing "dissection." Transmural flow was reversed at stenotic sites, passing from wall to stream. The development of plaques depended on the local pressure drop produced by high velocity of the stream. These studies suggest that physical factors affecting growth and metamorphosis of elements of the blood vessel lining may result in vascular sclerosis and stenosis.

11:40 Discussion

11:45

12. The Role of Fibrin Thrombi in the Genesis of the Common White Plaque in Arteriosclerosis

Daria M. Haust, Henry Z. Movat and Robert H. More. From the Department of Pathology, Richardson Laboratory, Queen's University, Kingston, Ontario, Canada.

A year ago we presented the morphologic appearance of various early arteriosclerotic lesions and their further evolution. It was shown that one way by which arteriosclerosis develops and progresses, is the deposition of mural fibrin thrombi and their incorporation into the arterial wall.

In our studies since then, we have attempted to define the significance and incidence of mural fibrin thrombi in the genesis of the common white arteriosclerotic plaque of the aorta. White opaque plaques could be identified microscopically as recent fibrin thrombi. Pearly white plaques were composed of a young, acid mucopolysaccharide-rich connective tissue, containing capillaries, numerous young smooth muscle cells and remnants of unorganized thrombus. Newly formed collagen and elastic fibers were present in the polysaccharide-rich tissue, mainly around capillaries and smooth muscle cells. In still other plaques the AMP material was almost entirely converted into collagenous tissue. It was concluded that these various microscopic pictures represent stages in the organization of mural fibrin thrombi—older thrombi, completely converted into connective tissue at one end, and recent thrombi composed almost exclusively of fibrin and cells at the other end of the scale. The outcome of this process is the formation of a fibrous plaque, the origin of which is difficult to determine, when the steps in its development from recent thrombi are not evident.

White fibrous plaques were studied in 29 aortae. Thirteen of these presented direct evidence of thrombotic origin in the form of remnants of unorganized thrombus material within the organizing plaques. A total of 58 plaques were studied and of these, 24 showed evidence of thrombotic origin. Since all transitions between plaques in various stages of organization with and without remnants of fibrin thrombus material were encountered, it was concluded that all fibrous white plaques studied probably arose on the basis of mural fibrin thrombosis. Sometimes these white fibrous plaques overlay atheromatous lesions. However, no conclusions were possible as to the relationship of the mural fibrin thrombi to the genesis of the atherosclerotic lesions in these cases.

11:55 Discussion

12:00

Luncheon, Guest Lecturer, Donald Mainland

Safety in Numbers

2:00

Business Session

2:30

Presidential Address, Arthur C. Corcoran

SUNDAY AFTERNOON

Charles F. Wilkinson, Jr., Presiding

3:00

13. Essential Fatty Acids, Lipid Transport, and Degenerative Vascular Disease

Laurance W. Kinsell, George D. Michaels, Roger W. Friskey, Frederick R. Brown, Jr. and Fudeko Maruyama. From the Institute for Metabolic Research of the Highland Alameda County Hospital, Oakland, Calif.

Recent studies from this laboratory have implemented the concept that an optimal supply of essential fatty acids is essential for the maintenance of a normal level of plasma lipids. A recent study, carried out under quantitatively controlled conditions, in which synthetic triglycerides have been used as the only source of dietary fat, provides further confirmation.

The fatty acids esterified with cholesterol normally are unsaturated fatty acids. Unavailability of sufficient essential fatty acid appears to result in excessive cholesterol production, elevation of plasma cholesterol, and abnormal deposition of cholesterol.

The precise metabolic role of essential fatty acids is still unclear, but among the factors which influence essential fatty acid requirements are the following: (1) Dietary intake of saturated fat and saturated fat precursors; (2) dietary cholesterol; (3) "maleness," (in male animals, the essential fatty acid requirement is 4 to 7 times that of the female); (4) dietary vitamin B-6; (pyridoxal is required to synthesize arachidonic acid from linoleic acid); (5) dietary methionine.

Data and interpretations relating to the above will be presented.

3:10

14. The Nature of the Plasma Cholesterol Elevating and Depressant Factors in Butter and Corn Oil

J. M. R. Beveridge, W. F. Connell and G. A. Mayer. From the Departments of Biochemistry and Medicine, Faculty of Medicine, Queen's University, Kingston, Ontario, Canada.

Three dietary experiments have been performed in which 52, 48 and 38 male students and staff members participated as experimental subjects. In each study, everyone consumed the same homogeneous formula diet for 8 days at which time they were divided into comparable groups comprising 7 to 9 individuals per group. One group was maintained on the original diet for a further 8 days and the others were given diets varying in respect of the level and nature of the fat moiety or of fat-soluble supplements.

In the first experiment 52 subjects ingested for 8 days a diet in which butter fat provided 60 per cent of calories. The plasma cholesterol remained essentially constant and did not change significantly in those continuing on this diet for a further 8 days. The other groups were given the same diet supplemented with 10 mg. α-tocopherol, 200 mg. α-tocopherol, or 7 Gm. β-sitosterol/950 calorie portion. The supplements of α-tocopherol had no effect, but the β-sitosterol brought about a highly significant decrease in plasma cholesterol. An explanation for this response in normocholesterolemic individuals will be offered.

In the second experiment 48 subjects consumed for 8 days a diet in which butter fat provided 60 per cent of calories. The subjects were divided into groups and transferred to diets in which 30 per cent of calories were supplied by butter fat and 30 per cent by various corn oil fractions obtained by high vacuum molecular distillation (supplied by the Distillation Products Industries of Rochester, N. Y.). All groups showed highly significant decreases in plasma cholesterol, the largest drop being noted in the case of the most volatile fraction derived from the corn oil.

In the third experiment 38 subjects ingested for 8 days a diet providing 60 per cent of calories from corn oil. The subjects were divided into groups and transferred to diets supplying 40 per cent of calories from butter oil or various butter oil fractions obtained in the manner described above. All groups showed highly significant increases, the greatest increase being noted in the case of the most volatile fraction.

3:20 Discussion

3:30

15. Biliary Tract Lesions and Production of Gallstones in Rabbits Fed 3β-Cholestanol

Margaret Bevans and Erwin H. Mosbach. From the Columbia University Research Service, Goldwater Memorial Hospital, and the Departments of Biochemistry and Medicine, Columbia University, New York, N. Y.

Thirty rabbits maintained for from 8 to 42 days on a diet containing 0.25, 0.50, or 1% 3β-cholestanol developed inflammatory lesions of the gallbladder and large bile ducts, cloudy bile and cholelithiasis. The gallbladders of all these animals contained spherical concretions which, in the experiments terminated after 21 to 42 days, had coalesced to form stones that distended the gallbladder and the intra and extrahepatic ducts. The stones consisted largely of glycodeoxycholic and glycocholic acids and

ontained only traces of sterols, calcium salts or ile pigments. In rabbits killed after 8 days of 3β-holestanol feeding, the lamina propria of the gall-bladder and bile ducts was edematous and infiltrated with lymphocytes and histiocytes. The severity of the inflammatory reaction was only slightly greater after 42 days on the diet. Neither atherosclerosis nor lipid infiltration of the aorta was present in the rabbits fed 3β-cholestanol. The addition of 0.5 per cent cholesterol to the diet containing 0.5 per cent 3β-cholestanol did not alter the pathologic changes in the biliary tract produced by 3β-cholestanol alone. Gallstones were also produced in mice with diets containing 3β-cholestanol for 4 months. These findings may justify caution in the use of 3β-cholestanol, which prevents hypercholesterolemia in cholesterol-fed animals and has been considered as a possible agent for the treatment of human hypercholesterolemia. Cook, Kliman, and Fieser, (Arch. Biochem. Biophys. **52:** 439, 1954), reported murky bile or gallstones in 2 of 4 rabbits fed 3β-cholestanol but did not describe histologic changes.

3:40

16. Metabolism of Cholesterol and 3β-Cholestanol in Rabbits

E. H. Mosbach, L. L. Abell and F. E. Kendall. From the Columbia University Research Service, Goldwater Memorial Hospital, and the Departments of Biochemistry and Medicine, Columbia University, New York, N. Y.

Rabbits absorb considerable amounts of dietary cholesterol and 3β-cholestanol. Balance studies were undertaken in this species to determine whether any significant amounts of the absorbed sterols were metabolized to bile acids or other products and excreted in the feces. The following results were obtained: 1. On a low-fat, sterol-free stock diet rabbits excreted 133 mg. of sterol and 160 mg. of bile acids daily. 2. When the stock diet was supplemented with 0.77 per cent of cholesterol the fecal sterols accounted for 49 per cent of the intake after 1 week and for 89 per cent after 13 weeks of feeding. There was no increase of bile acid excretion in response to cholesterol feeding. 3. When 0.9 per cent of 3β-cholestanol was added to the stock diet, 89 per cent of this sterol was recovered after 3 weeks. The bile acid excretion remained at the control level. 4. On diets containing 12 per cent triolein in addition to cholesterol or 3β-cholestanol, the excretion of sterols and bile acids was as the same as on the low fat diets, but tissue deposition of these sterols was increased. These findings suggest that in rabbits excess dietary sterols are largely disposed of by fecal excretion, after the tissues have reached saturation.

3:50 **Discussion**

4:00

17. Epidemiological Studies of Atherosclerosis among Men and Women of Different Ethnic Origins in the New York Clothing Industry

Frederick H. Epstein, Rita Simpson, Ernst P. Boas, J. Murray Steele, David Adlersberg and John W. Fertig. From the Research Department of the Sidney Hillman Health Center, New York, N. Y.

The sample studied consisted of 604 men and 515 women of Italian or Jewish parentage, age 40 and over, chosen at random from a population of 32,000 clothing workers who were comparable with regard to working conditions, socioeconomic status and diet. The age-adjusted prevalence of manifest coronary heart disease was 7.3 per cent and 3.5 per cent, respectively, among Italian men and women; and 14.2 and 3.5 per cent, respectively, among their Jewish counterparts; an ethnic difference was thus confined to the men.

The atherogenic effects of serum cholesterol, blood pressure and weight levels were studied by determining the frequency of manifest disease within upper and lower ranges of these variables (i.e. above and below the third quartile). Among Italian men, the prevalence of coronary disease was approximately twice as high in the upper as in the lower range of each of these 3 variables; when the levels of all 3 factors were low, the prevalence among this group was reduced to only 2 per cent. Among Jewish men, however, coronary disease prevalence appeared largely unaffected by these 3 variables, singly or combined. Similarly, the frequency of roentgenographic evidence of aortic calcifications was enhanced by these 3 factors only among Italian but not Jewish men; the same ethnic difference, though less marked, was observed among the women.

Thus, measures designed to lower the prevalence of these particular atherogenic factors might vary in effectiveness among different segments of the general population. Presently unknown or merely suspected atherogenic factors beyond those studied here may be of considerable quantitative importance among predisposed groups, such as the Jewish men and women in this sample.

4:10 **Discussion**

4:15

18. The Distribution of Atherosclerosis in 200 Autopsies with Special Reference to the Location and Severity of the Vascular Lesions

*James Roberts and Campbell Moses. From the University of Pittsburgh School of Medicine, Pittsburgh, Pa.**

Detailed morphologic studies of all the accessible arteries in patients coming to autopsy from any

* This work was aided in part by a grant from the John A. Hartford Foundation.

cause have been made. All lesions grossly visible have been graded as to their extent and severity. In addition, the pertinent clinical data from the history, physical examination and laboratory studies have been correlated with the morphologic and autopsy findings. Particular attention is paid to the body weight–organ weight ratios and the severity of the atherosclerotic lesions. Major emphasis is placed upon the widespread distribution of benign, asymptomatic atherosclerosis and this is contrasted with the disastrous complications that follow the disruption of a small lesion at a critical location within a vital structure.

4:25 Discussion

4:30

19. The Significance of Intramural Hemorrhages in Coronary Atherosclerosis

John D. Hamilton and J. H. Mowbray. From the Department of Pathology, University of Toronto, Toronto, Canada.

Since Paterson described intimal vascularization and hemorrhage in atheroma, there has been considerable difference of opinion regarding the role of such hemorrhages in the pathogenesis of thrombosis, especially of the coronary arteries. With the objective of determining the incidence of such hemorrhages and their significance in producing arterial occlusion and in contributing to the atherosclerotic process, the hearts from 100 consecutive adult autopsies at the Toronto General Hospital were examined by the perfusion and clearing technic of Durlacher. This permits a complete gross examination of the whole coronary tree down to vessels of 1 mm. caliber, and has the advantage of facilitating subsequent microscopic examination.

The majority of these cases fell between the ages of 50 and 80 years, and showed atherosclerosis from grades I to IV in 88 cases. In 35 cases there was myocardial damage attributable to coronary atherosclerosis. Intimal hemorrhages were found in 51 cases, including most of the 35 cases mentioned above.

Intimal hemorrhages only occurred in atheroma of grade III (soft necrotic plaques) or greater, and were not necessarily associated with vascularization from the lumen. In those cases where there was recent thrombosis of the lumen and hemorrhage in the underlying plaque, continuity of hemorrhage and thrombus could be traced by serial section in those cases studied by this method. One could not determine whether the intramural hemorrhage originated from the lumen and was due to rupture of a soft plaque with excavation by blood under pressure, or represented a prima facie hemorrhage from intramural capillaries and subsequent rupture of the plaque with superimposed thrombus formation. Correlation of the hemorrhages with the clinical state of the patient is discussed, as well as the limiting factors in intramural hemorrhage as a cause of vascular occlusion.

4:40 Discussion

4:45

20. Two Forms of Necrotizing Arteritis in Dogs Related to Renal Insufficiency

Henry C. McGill, Jr., Jack C. Geer and Russell L. Holman. From the Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.

Previous reports from this laboratory have been concerned with a form of necrotizing arteritis in dogs that have been subjected to a combination of high fat diet and renal insufficiency. Other workers have described a wide variety of lesions occurring in dogs with renal insufficiency, which are not dependent on any dietary factor. Re-evaluation of the material accumulated in this laboratory, together with the study of several nephrectomized dogs whose survival time was prolonged by dialysis on the artificial kidney, has made it possible to differentiate between 2 distinctly different forms of arteritis. One form involves primarily focal necrosis of the smooth muscle of muscular arteries and arterioles. It occurs in a high percentage of nephrectomized dogs which survive 4 days or longer, and in a lesser percentage of dogs subjected to renal injury by uranium nitrate. Others have shown that this lesion does not depend on hypertension or retention of any measurable waste products in the blood, and that the acute lesions closely resemble those of human malignant nephrosclerosis. For convenience, since the tissue predominantly affected is smooth muscle, it is suggested that this characteristic lesion be referred to as *myoarteritis.*

The other form of arteritis involves the interstitial connective tissues of large musculoelastic arteries (aorta, pulmonary artery, and endocardium of the left atrium). It occurs in approximately 80 per cent of dogs subjected to uranium nephrosis or bilateral nephrectomy if the dogs have been fed a diet rich in creamery butter for 8 weeks or longer. In this lesion smooth muscle does not undergo degenerative changes until relatively late, and to distinguish it from myoarteritis, it is suggested that it be referred to as *mucoarteritis.*

It can be concluded that the functional integrity of the kidney is essential to the maintenance of a variety of tissues of the body. Although our knowledge of the specific renal factors responsible for the integrity of these tissues is extremely meager, it can be clearly shown that certain factors preceding the renal injury—in this instance, diet—can alter the pattern of tissues affected.

4:55 Discussion

6:30–7:30

Reception for the Ten Past Presidents and Their Ladies

MONDAY MORNING NOVEMBER 12, 1956

Forrest E. Kendall, Presiding

8:30 Registration

9:00

21. Endothelial Regeneration

C. Bruce Taylor, George E. Cox, Marjorie A. Stumpe and Milton Weinberg. From the Rush Laboratories of Pathology and Surgical Research, Presbyterian Hospital, Chicago, Ill.

The rate of regeneration of endothelium has been studied in vivo in aortas of dogs following mechanical denudation of measured areas of endothelium and minimal subendothelial tissue. The lower abdominal aorta was approached through a midline incision in anesthetized dogs. After isolation from the circulation with arterial clamps and provisional ligatures, anterior longitudinal incisions, 5 to 8 cm. long, were made and intimal lesions were placed on posterior aortic walls. Margins of lesions were marked by gently applying and rotating the cutting edges of cork-borers with diameters of 2 to 5 mm. Endothelium within the marked zones was denuded by rubbing the encircled area with an eraser. The aortic incision was closed with 2 rows of arterial silk and the arterial circulation through the segment, restored. Animals were sacrificed sequentially. Endothelial regeneration was studied by employing the endothelial surface method described by Lautsch, McMillan and Duff (Lab. Invest. **2:** 397, 1953). The more superficial lesions were promptly covered with a thin, clear fibrinous clot while deeper, rougher lesions were covered with a slightly raised mixed clot. No evidence of endothelial regeneration was seen at the margins of denuded lesions 2 to 6 days old. Lesions 8 days old had tongue-like projections of endothelial cells extending inward from the margins. At 10 days circular lesions with 4 to 5 mm. diameters were about half covered with regenerated endothelium. Lesions 12 and 14 days old were about 80 per cent covered with endothelium. At 16 and 21 days, all lesions still had small central defects. In 28 and 45 day old lesions, complete endothelial regeneration was generally observed but a few of these lesions still had a small central defect.

9:10 Discussion

9:15

22. The Effect of Vascularization on Lipid-Connective Tissue Reactions in the Cornea

L. L. Waters. From the Department of Pathology, Yale University School of Medicine, New Haven, Conn.

Necrosis, hemorrhage and ulceration in atheromas of the arterial wall lead to important complications of arteriosclerosis. In the present experiments, dog corneas have been used as a model system in the study of these phenomena. Chylomicrons and other pertinent plasma lipids have been injected into the avascular central area of the cornea. This procedure results in an incomplete inflammatory reaction on the part of the corneal tissue consisting, with some variation, in collagen damage, the appearance of mononuclear phagocytes and more or less foam cell accumulation. There is gradual removal of a portion of the injected lipid substance. At about 10 days to 2 weeks after the injection of lipid into the cornea the margin of the injected ares becomes vascularized by new capillaries growing in from the limbus. This provides opportunity for the study of the effect of vascularization on connective tissue containing lipid. In some instances it has been observed that when the new vascular channels reach the margins of the intracorneal lipid deposit, edema and cellular exudation occur. Necrosis and hemorrhage follow and ulceration of the corneal surface may take place. Foam cell accumulation is now massive and lipid removal is accelerated. Many of the degenerative and inflammatory changes that occur in late human arteriosclerosis are duplicated.

9:25 Discussion

9:30

23. The Effects of Augmented Cholesterol Intake on the Lipids of Connective Tissue

Nancy L. Noble and Robert J. Boucek. From the Miami Heart Institute, University of Miami School of Medicine, Miami, Fla.

Connective tissue has distinctive lipid features, of which the most noteworthy is the large concentration of cholesterol. This report will describe the response of rabbit connective tissue to large amounts of dietary cholesterol.

Serial determinations of cholesterol concentration of connective tissue were made possible by implantation of 10 sponges along the dorsum of a rabbit. The connective tissue was fractionated into saline-soluble (globular protein) and saline-insoluble (fibrous protein) portions.

After 14 days on augmented cholesterol intake, there was a sharp rise in tissue lipids which consisted of increases in total and choline-containing phospholipid, total and ester cholesterol, and neutral fat. After 45 days, serum cholesterol was 945 mg.

per cent and connective tissue total cholesterol, 1200 mg. per cent (control values, 30 mg. per cent and 193 mg. per cent respectively).

On reinstitution of regular laboratory chow, tissue total lipid values stabilized and concentrations of phospholipids and neutral fat slowly receded to pretreatment levels. However, cholesterol concentration continued to rise in spite of a 15-fold reduction in serum cholesterol. After 4 months on the regular chow, tissue total cholesterol was 4000 mg. per cent and the sponge-biopsy resembled, grossly and microscopically, an atheroma or xanthoma.

Kinetic analyses of the data indicate a marked avidity of connective tissue for cholesterol. Partitioning of the elevated tissue cholesterol into saline-soluble and saline-insoluble fractions reveals that the soluble portion reflects promptly the elevation of serum cholesterol whereas the fibrous or insoluble fraction responds at a much slower rate. Upon return of the animal to a regular laboratory diet, concentration of the saline-soluble cholesterol stabilizes, but cholesterol concentration in the insoluble fraction continues to rise. With a serum cholesterol equal to the prefed level and cholesterol concentration in the saline-soluble fraction elevated but constant, cholesterol incorporation into fibrous protein occurs at a rate similar to that when cholesterol concentration of the saline-soluble fraction is not elevated by augmented cholesterol intake.

9:40 Discussion

9:45

24. Effect of High Fat and High Protein Diets on Tissue Lipids

Helen B. Brown and Lena A. Lewis. From the Research Division of the Cleveland Clinic Foundation and Bunts Educational Institute, Cleveland, Ohio.

Dietary constituents other than cholesterol influence the cholesterol level of the body. The effect of excess fat in the absence of cholesterol is recognized. The role of dietary protein is not as well defined, although hypercholesterolemia and atherosclerosis have been elicited by feeding an incomplete protein. We have found that hepatic cholesterol concentration is decreased during ingestion of a high protein diet.

Two diets were fed, composed of dried skim milk and either coconut or soy bean oil, and added vitamins. Skim milk made up 43 per cent (I) and 76 per cent (II) of the diet. These diets provided adequate protein (16 per cent and 28 per cent, respectively), and high fat (54 per cent and 22 per cent, respectively), with less than 0.1 per cent sterol. Thirty-five-day-old, male rats, weighing 75 to 95 Gm., were placed on these diets and continued for 10 to 12 weeks. Those on the high skim milk diet (II) ate more food and gained more weight. In terms of calories eaten per gram body weight gain, the food intake of the 2 groups was comparable. Consequently the rats on diet II consumed 3 times more protein and two-thirds less fat than those on diet I.

This high protein intake reduced hepatic total lipid and cholesterol independently of the type of fat fed; from 7.3 mg./Gm. liver to 4.5 mg. on coconut oil; 19 mg. to 10 mg. on soy bean oil. Serum lipid and protein levels were only slightly changed.

The character of the dietary fat affects hepatic cholesterol concentration profoundly; rats fed unsaturated soy bean oil had 2½ times more than those eating the saturated coconut oil diet. Those with the highest hepatic cholesterol, (II, soy bean oil), had a tendency toward low serum cholesterol.

The iodine number of the liver, serum and adipose tissue lipids changed with the iodine number of the dietary fat.

9:55 Discussion

10:00

25. The Effect of Various Chronic Levels of Dietary Casein on Hypercholesteremia in the Rat

Richard J. Jones and Sheldon Huffman. From the University of Chicago, Department of Medicine, Chicago, Ill.

In an effort to explore the various elements of the diet found by Wissler, Eilert, Schroeder and Cohen, to be atherogenic in the adult rat, 3 6-month dietary experiments have been performed. On this casein-lard diet the serum cholesterol rises at a rate depending apparently upon the level of dietary cholesterol, but the ultimate level reached after 2 to 4 months was independent of the dietary cholesterol or a twofold alteration in dietary fat level. On the other hand, the ultimate level of serum cholesterol seemed to be remarkably sensitive to the level of dietary protein and its quality.

Low levels of 9 per cent or 7½ per cent casein in the diet led to significantly higher levels of serum cholesterol than did 12.5 per cent or 18 per cent casein diets. Levels of 25 per cent or 40 per cent also led to a substantial hypercholesteremia, the animals on 40 per cent casein achieved a mean serum cholesterol of 490 mg. per cent after 6 months. Addition of gelatin to a low casein diet prevented the hypercholesteremia, and the use of gelatin alone led to no elevation of the serum cholesterol.

One difference between the hypercholesteremia seen at low levels of casein and that seen with high levels was the fact that the former tended to have lower cholesterol/lipid phosphorus ratios. The further fact that gelatin seems to lack the potential for promoting this hypercholesteremia leads to an interesting speculation as to the means by which hypercholesteremia occurs at chronic levels of

casein above or below a rather narrow optimum range. It becomes apparent that under these circumstances the chronic level of dietary protein is an important determinant of the serum cholesterol level.

10:10

26. **Dietary Protein, a Possible Protective Factor against Atherosclerosis**

T. Nishida, F. Takenaka, N. T. Rand and F. A. Kummerow. From the Department of Food Technology of the University of Illinois, Urbana, Ill.

Approximately 400 day-old chicks of known genetic strain were kept on a fat-free purified diet for 1 week. They were then divided into matched groups of 8 to 20 birds each, and kept on purified diets which contained 0.5 per cent cholesterol, all of the essential growth factors, 15 per cent fresh corn oil, either unheated or heated for 24 hours at 200 C., and 15, 20, 30 or 35 per cent purified soybean (Drackett) protein. The latter was added at the expense of the carbohydrate (Cerelose). A record of feed consumption was kept and the birds were weighed at weekly intervals.

At the end of 4 weeks the birds were bled via heart puncture, and the livers, hearts and aortas removed. The latter were stained with a saturated solution of Sudan IV in 70 per cent ethanol and examined for signs of atherosclerosis. The serum lipoprotein pattern was determined with a Spinco model E analytical ultracentrifuge and the serum cholesterol of individual birds was determined by the Sperry-Schoenheimer method.

The results indicated that dietary protein tended to prevent, while heated oil promoted, atherosclerosis. The birds which had been fed the low protein diets had a higher incidence of atherosclerosis, and higher serum cholesterol and lipoprotein levels than those on the high protein diets. Furthermore, those on the low protein diets had a more heterogeneous lipoprotein pattern and lipoproteins of higher S_f values than those on the high protein diets. Heated oil seemed to counteract the beneficial effects of dietary protein. Histologic examination indicated the presence of foam cells in the aortas of birds which had received heated fats but not in those on fresh oil.

10:20 **Discussion**

10:30

27. **The Effect of Various Estrogens and Estrogen Analogues on Serum Cholesterol and Lipid Phosphorus in Rats on an Atherogenic Diet**

Robert E. Priest, Marjorie T. Schroeder, Richard Rasmussen and Robert W. Wissler. From the Department of Pathology of the University of Chicago, Chicago, Illinois.

Interest in the use of estrogens in the clinical control of atherosclerosis prompted this study of the early effects of these substances on serum cholesterol and lipid phosphorus. Twenty-five adult male albino rats were fed a low protein diet containing 2 per cent cholesterol and 25 per cent corn oil; a ration which has previously been shown to cause lipid-containing lesions in the coronary arteries of the rat. The diet was fed by stomach tube in the amount of 12 ml. 3 times daily. After 1 week of this diet, groups of 5 animals each received daily subcutaneous injections of the following substances: (1) sesame oil; (2) 0.333 mg. estradiol, (3) 0.333 mg. diethylstilbestrol; (4) 0.333 mg. estriol; and (5) 0.333 mg. progesterone. Weekly determinations of cholesterol and lipid-phosphorus were made on pooled sera from each group for six weeks.

During the first week of feeding with no treatment there was a slight decrease in serum cholesterol and a greater (30 to 50 per cent) decrease in lipid phosphorus. Little change occurred during the first week of hormone administration, but by the end of the second week, definite differences between the various groups were evident. Serum cholesterol values in the group on diet alone had increased by about 25 per cent, while those of the groups which had received either estradiol or estriol had increased by about 100 per cent. Lipid phosphorus in the control group remained slightly depressed from the initial value, while that of the groups given natural estrogens had doubled. Both cholesterol and lipid phosphorus in the groups given natural estrogens remained higher than in the control group for the remainder of the experiment, with a lower cholesterol lipid phosphorus ratio. Values for both cholesterol and lipid phosphorus in the groups given diethylstilbestrol and progesterone did not differ remarkably from these values for the control group. Marked atrophy of the testes, prostate and seminal vesicles was found in all animals given estradiol, estriol or diethylstilbestrol, but was not apparent in the animals given progesterone or on diet alone.

These observations have been repeated in 2 experiments and are now being extended to other estrogen analogues.

10:40 **Discussion**

10:45

28. **Serum Lipid and Estrogenic Effects of Two New "Weak Estrogens" in Male Patients with Coronary Atherosclerosis**

*Roger W. Robinson, William D. Cohen and Norio Higano. From The Memorial Hospital, Worcester, Mass.**

This report is concerned with the clinical and serum lipid effects of 2 recently synthesized "weak

* This investigation was supported by grants from the G. D. Searle & Co.; Worcester District Chapter, Massachusetts Heart Association; and The Memorial Hospital Research Fund.

estrogens" (G. D. Searle & Co.) to determine whether a dissociation of estrogenic and lipid-altering effects occurs.

Serum lipid studies consisted of total cholesterol, lipid phosphorus, and electrophoretic and ultracentrifugal separation of α- and β-lipoprotein cholesterol. Data were obtained on 12 middle-aged male subjects with myocardial infarction at intervals during a control period of 1 year, with at least 2 studies performed within the final month. During the succeeding 8 months serum lipid studies were performed biweekly with monthly clinical evaluation. In the first 8-week period the subjects received orally 40–60 mg./day of SC-4289 [2,2-dimethyl-3-(-6′-benzyloxy-2′-naphthyl)pentanol]. An 8-week control period followed, with placebo tablets substituted. A second 8-week therapy period ensued, with SC-6924, (a derivative of estrone), at 50 mg./day orally. This was succeeded by another 8-week placebo control period.

During the trial with SC-4289 there were no effects on either serum total cholesterol or cholesterol partition between α- and β-lipoproteins. However, there was a significant increase of phospholipid, maximal at 4 weeks (mean: plus 26 mg. per cent) decreasing to the initial value at the end of treatment. This decrease continued for 4 more weeks (mean: 24 mg. per cent below initial value), followed by an increase to the pretreatment level within 2 weeks. The c/p ratio changed reciprocally. Clinically, there was no evidence of estrogenic effects.

The administration of SC-6924 produced a statistically significant fall in serum total cholesterol, maximal after 4 weeks (mean: minus 34 mg. per cent). There was a highly significant mean decrease in c/p ratio from 1.20 to 0.96. The fraction of cholesterol in the α-lipoproteins increased to a plateau at 4 weeks; an apparent reciprocal decrease in the β-lipoprotein cholesterol fraction was not significant. The resultant decrease of the β-/α-lipoprotein cholesterol ratio, from 5.6 to 2.9 in 6 weeks, was highly significant. Clinically, 7 of the 12 subjects showed no estrogenic effects after 8 weeks of treatment. Of the 5 subjects who showed slight gynecomastia, 2 suffered nausea, vomiting, anorexia, malaise and weakness; 1 developed dyspnea and increased angina; 1, loss of libido. These effects disappeared within 4 weeks after cessation of therapy in all subjects. In contrast, in a previous study of 20 similar patients given 10 mg. daily of oral Premarin, the serum lipid changes were similar, but estrogenic effects were noted in all subjects after 6 weeks of treatment. A 20 mg./day dosage level of SC-6924 is being evaluated in the same group of 12 subjects, and these results will be presented.

10:55 Discussion

11:00

29. Serum Lipid and Lipoprotein Concentrations in Castrate and Noncastrate Institutionalized Male Subjects

R. H. Furman, R. P. Howard and R. Imagawa. From the Cardiovascular Section of the Oklahoma Medical Research Foundation, and the Department of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

The incidence and severity of coronary atherosclerosis, both clinically and anatomically, has long been recognized as more severe in males than females. Noteworthy are the observations of White and Gertler that male castrates suffer a less severe form of the disease than do noncastrates.

This study was undertaken to ascertain in what manner the serum lipids and ultracentrifugally determined lipoproteins of castrate and noncastrate males differed. All 44 subjects were inmates of a state institution for the mentally deficient, but otherwise in apparent good health. Twenty-four eunuchs from 23 to 79 years of age were compared with 20 noncastrate controls of similar ages. The number of sera from castrates was 125, from controls 69.

Significant differences existed between the mean values of the serum lipids of the two groups.

Castrates had lower $-S_{1.21}$ 25–40 β-lipoprotein levels: 197 mg. per cent $\pm$ 44.6 vs. 239 mg. per cent $\pm$ 65.4 ($0.05 > p > 0.01$). Castrates had higher values for the ratio ($-S_{1.21}$ 0–12/$-S_{1.21}$ 25–40) α/β-lipoprotein levels: 1.24 $\pm$ .41 vs. 0.90 $\pm$ .25 ($p < 0.01$). This was also true for the ratio

($-S_{1.21}$ 0–12/total cholesterol)

(α-lipoprotein/total cholesterol): 1.30 $\pm$ .21 for castrates vs. 1.12 $\pm$ .31 for controls ($0.05 > p > 0.01$), as well as for the ratio ($-S_{1.21}$ 0–12/lipid P $\times$ 25) (α-lipoprotein/phospholipid): 0.95 $\pm$ .14 vs. 0.76 $\pm$ .20 ($p < 0.01$).

Castrates had higher levels of $-S_{1.21}$ 0–12 α-lipoproteins, but the difference was less significant: 223 mg. per cent $\pm$ 33.1 vs. 203 mg. per cent $\pm$ 65.5 ($0.50 > p > 0.05$). No significant differences were noted between mean serum levels of total cholesterol, phospholipids or the degree of esterification. Higher values for the ratios phospholipid/total cholesterol and phospholipid/free cholesterol were noted in the castrates, but the significance was not great ($0.50 > p > 0.05$).

There was no significant difference between the levels of $-S_{1.21}$ 40–70 (S_f 10–20) lipoproteins or $-S_{1.21}>70$ (S_f 20–100) lipoproteins.

It must be kept in mind that these are mean values and that attention has not been paid here to the age of the subject at castration nor to the levels of urinary 17-ketosteroid or gonadotropin excretion.

The serum lipid pattern distinguishing the eunuch

may be causally related to his relative freedom from coronary atherosclerosis.

11:10 Discussion

11:15

30. The Effect of Estrogens on Spontaneous and Experimental Atherosclerosis in the Rat

M. R. Malinow and A. A. Pellegrino. From the Pabellón de Cardiología "Luis H. Inchauspe," Hospital Ramos Mejía, Buenos Aires, Argentina.

Four groups of adult white male rats of the Williams strain, reared on a standard laboratory diet, were studied. Ten animals received 5 to 10 γ of α-estradiol benzoate intraperitoneally. Forty-one rats in which unilateral cellophane perinephritis was induced received, in addition, 5 ml. sunflower-seed oil (I.N. 130), of which 18 also received 5 to 10 γ of α-estradiol benzoate. These procedures were carried out daily (except Sundays) for periods up to 60 days. Thirty rats (previously described in Arch. Path. **61:** 11, 1956), were used as controls.

Multiple sections of the aorta and its primary branches (intercostal, mesenteric, etc.) the coronary and the renal arteries were studied histologically. Rats showing intimal lipid infiltration and/or intimal proliferation were considered as positive for atheromatosis and/or atherosclerosis respectively; intimal changes were graded from 0.5 to 3.0 (cf. supra). None of the rats of the first group showed any arterial intimal lesions as compared with 17 (54 per cent) of the control rats showing minimal changes. Eighteen rats (43 per cent) of the second group and 5 (27 per cent) of the third showed lesions. The difference between the first group and the control was statistically significant ($p < 0.01$); although the difference between the second and third was not, ($p > 0.2$). When the intimal changes were graded in the different vessels, it was seen that estrogens reduced the number of lesions in the aorta and its primary branches.

11:25 Discussion

11:30

31. Effects of a Thyroxine Analogue on the Cholesterol-Fed Rat

Charles H. Duncan and Maurice M. Best. From the Department of Medicine of the University of Louisville School of Medicine, Louisville, Ky.

A thyroxine analogue, 4-(3′,5′-diiodo-4′-hydroxyphenoxy)-3,5-diiodo-benzoic acid, in which a carboxyl group is substituted for the alanine side chain of thyroxine, has been administered to cholesterol-fed rats, and its effects on serum and liver cholesterol observed. The activity of the analogue in preventing thiouracil-induced goiter has also been studied.

In the 1 per cent cholesterol and 0.5 per cent thiouracil-fed rat the daily subcutaneous administration of 2 mg./100 Gm. failed to prevent goiter, the mean thyroid weight at 14 days being 15.7 mg./100 Gm. (saline-injected control 16.7). Definite inhibition of cholesterol accumulation in the liver was observed, however, the analogue-injected animals having a mean liver cholesterol of 313 mg./100 Gm. liver (control 1042).

In a comparable study l-thyroxine, in the dose of 3 μg./100 Gm. effectively prevented the development of goiter, the mean thyroid weights being 7.6 mg./100 Gm. (6.5 normal). Thyroxine at this dose had only slight effect on liver cholesterol, the mean being 796 mg./100 Gm. (control 1042).

Oral administration of the analogue for 42 days to cholesterol-thiouracil-fed rats revealed it to be active by this route. Mean liver cholesterol was 395 mg./100 Gm. (control 1481) and mean serum cholesterol 115 mg./100 ml. (control 179).

Comparable effects were noted on liver cholesterol of euthyroid (nonthiouracil-fed) rats. That this effect of the analogue is due to accelerated loss of cholesterol from the liver is indicated by the results of its administration to rats previously "loaded" with cholesterol.

It is concluded that this analogue of thyroxine prevents the accumulation of cholesterol in serum and liver in the cholesterol-fed rat. It differs from thyroxine in that it exerts this effect on cholesterol at a dosage that is ineffective in preventing thiouracil goiter.

11:40 Discussion

11:45

32. Correlative Histochemical - Serum Lipid Studies of Experimental Atherogenesis in I^{131}-Treated, Cholesterol-Fed Dogs

I. Ernest Gonzales, Loyal L. Conrad, Leonard N. Norcia and Robert H. Furman. From the Cardiovascular Section, Oklahoma Medical Research Foundation and the Departments of Medicine and Anatomy, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Severe hypothyroidism was induced in 10 dogs with I^{131}. Eight dogs were fed cholesterol, 10 Gm. daily for at least 18 months. Three cholesterol-fed dogs and the 2 control animals exhibited hypercholesterolemia less than 5 times mean pretreatment levels. In these animals the arterial bed was not remarkable save for minor atherosclerotic coronary cushions. The liver was histochemically normal except for small foci of increased cholesterol throughout the parenchyma.

The remaining 5 dogs exhibited hypercholesterolemia 7 to 12 times control levels. Their coronary arteries contained massive atheromatous plaques. The abdominal aorta was severely involved; the

thoracic aorta evidenced atheromas at intercostal artery orifices. The aortic arch was almost intact. Widespread and early involvement of the vasa vasorum was noted.

Only the livers of the 5 dogs exhibiting marked atherosclerosis were significantly altered. Large vacuolated hepatic cells were noted and the lipid within these cells was reduced. Marked increase in hepatic cell glycogen was noted. The adrenals exhibited turgid spongiocyte-like cells and the kidneys contained numerous fatty casts.

Without exception the degree of experimental atherosclerosis in the I^{131}-treated dog was correlated with the degree of hepatic alteration, as well as with the degree of hypercholesterolemia or hyperphospholipemia. Dogs with intact livers in this study did not develop significant atherosclerosis.

The natural history of experimental atherosclerosis was studied using histochemic technics for polysaccharides, cholesterol, total lipid, masked lipid and amino acid functional groups. Intimal edema appears first, followed by an accumulation of PAS-positive intercellular substance (principally neutral polysaccharides). With progressive chronicity, metachromasia ("acid polysaccharides") develops at the site of "injury," while PAS-positive substances diminish. Lipid accumulation then becomes evident. In addition to cholesterol, both neutral and acid polysaccharides, glycogen and protein moieties contribute significantly to the formation of the atheroma. Atheromas exhibiting intense metachromasia stain weakly for amino acid groups, while intensely PAS-positive areas stain readily for these groups.

11:55 Discussion

12:00

Luncheon

MONDAY AFTERNOON

J. C. Paterson, Presiding

2:00

33. The Effects of Adrenalectomy on Serum Lipid Levels in the Human

Daniel A. Sherber and Martin Marcus. From the Metabolic Research Laboratory of Fordham Hospital, New Rochelle, N. Y.

Following surgical ablation of the adrenal glands and gonads for breast cancer in male and female patients, the following changes were observed: A steady increase in serum cholesterol from normal levels to amounts exceeding 400 mg. per cent, phospholipids similarly increased but at a lesser pace resulting in an altered cholesterol/phospholipid ratio; total lipids increased as well as neutral fats, but at no time was there a visible lipemia. Several weeks post-surgery were needed before the maximum effects were observed. These changes were independent of maintenance cortisone therapy as seen in the control group. The most striking change noted was in the freely extractable cholesterol of Macheboeuf. About 10 per cent of the total cholesterol is extractable by this method in the control groups which increased to about 50 per cent in the adrenalectomized human. Parallel changes were noted in a case of Addison's disease studied. All patients studied had normal renal, hepatic, cardiac and respiratory functions as determined by laboratory tests. These patients also failed to demonstrate clinical or laboratory evidence of metastases.

2:10 Discussion

2:15

34. Atherogenic Effects of Insulin Combined with Adrenal Hormones in Cholesterol-Fed Chicks

J. Stamler, R. Pick and L. N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Previous experiments from this department indicated that insulin counteracted the protective effect of estrogens on coronary atherogenesis. It also abolished regression of lesions usually occurring after cessation of cholesterol feeding. The present experiment was undertaken to analyze further the parameters and mechanisms of this insulin-atherogenic effect. Eight groups of birds (age 14–21 weeks) were studied, all on a diet of mash supplemented with 2 per cent cholesterol + 5 per cent cottonseed oil (2 CO): (1) 2 CO control, (2) 2 CO + insulin, (3) 2 CO + insulin + adrenalin, (4) 2 CO + insulin + hydrocortisone; (5), (6), (7) and (8)—the foregoing plus estrogens All groups receiving insulin tended to eat less food and gain less weight than the controls. Insulin hypoglycemia tended to be counteracted by both adrenalin and hydrocortisone. Plasma cholesterol levels were similar in all groups except for intensification of hypercholesterolemia in birds receiving hydrocortisone. Incidence of gross aorta lesions was apparently increased in all insulin-treated groups. Coronary atherogenesis was intensified in all insulin-treated groups not receiving estrogens (groups 2, 3 and 4). It was particularly severe in the insulin + hydrocortisone-treated birds (group 4). All the insulin-treated groups receiving estrogens tended to exhibit partial counteraction of estrogen protection. These observations confirm and extend previous findings on the atherogenic effects of insulin, and demonstrate the severe atherogenicity of insulin plus adrenal hormones. They pose basic

problems concerning exogenous insulin as a possible atherogenic factor in diabetic patients.

2:25 Discussion

2:30

35. Effects of Heparin In Vivo and In Vitro on Serum Phenol Turbidity Test and Relation to the Clearing Mechanism

A. Scanu, L. A. Lewis and Michael C. Schotz. From the Research Division of the Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Kunkel, Ahrens and Einsemenger observed in 1948 that addition of phenol to human serum induces a turbidity which seemed to be related to the serum lipid content. Since heparin affects the distribution of serum lipids, when given in vivo, we studied the effect of heparin on the phenol turbidity test.

The test consists of mixing 0.5 ml. of serum with 4.5 ml. of 0.85 per cent NaCl and 1.0 ml. of 5 per cent phenol in saline. The samples were then allowed to stand at 4 C. for 2 hours and the turbidity then measured as optical density at 660 millimicra in a Coleman Junior spectrophotometer.

Samples taken after injection of heparin (35 units/Kg.) into normal human subjects yielded lower turbidities than samples taken prior to heparin injection. When phenol was added to solutions of β-lipoproteins prepared by ultracentrifugation at specific gravity 1.063, the samples developed less turbidity when obtained from postheparin than from preheparin sera.

Addition of phenol to sera containing varying amounts of heparin added in vitro induced an increased turbidity which appeared to be proportional to the amount of heparin added. No turbidity was noted when phenol was added to a heparin solution not in the presence of serum. The mechanism of this unexpected reaction is not yet apparent.

The decreased turbidity of serum samples obtained after injection of heparin is associated with the changes in lipoprotein distribution effected by activation of the clearing mechanism, although this may not be causal.

2:40 Discussion

2:45

36. Pancreas and the Production of Lipemia Clearing Factor

June L. Hadley and H. C. Meng. From the Department of Physiology, Vanderbilt University School of Medicine, Nashville, Tenn.

The presence of a lipemia clearing factor in the plasma obtained after injection of heparin is well documented. However, the mechanism of its production is still obscure. The object of the present study was to investigate the possible role of the pancreas in the production of this clearing factor. Young adult male rats of the Sprague-Dawley strain were used. The dosage of heparin was 0.05 mg./Kg. administered intracardially, unless otherwise specified. All blood samples were withdrawn 3 to 5 min. after heparin. The clearing activity of plasma was determined by measuring the decrease in optical density of a buffer system containing plasma and fat emulsion. This system was incubated at 37 C. for 2 hours. The observations made were as follows: 1. The clearing activity of postheparin plasma of uncontrolled alloxan diabetics receiving 0.05 mg./Kg. of heparin was markedly decreased to a value less than that of the nonheparinized plasma of the normal animal; increase in heparin dosage to 2.0 mg./Kg. did not appreciably enhance the activity. 2. Insulin corrected diabetes, but failed to improve the clearing activity of postheparin plasma significantly. 3. Insulin-regulated alloxan diabetics fed a diet containing 5 per cent lyophilized beef pancreas for a period of 4 to 6 weeks exhibited a postheparin plasma clearing activity slightly higher than that of the normal; treatment for 11 and 16 days was found to be as effective as for longer periods. 4. Postheparin plasma of insulin-regulated diabetics fed a diet containing 0.5 per cent Lipormone (Choay) possessed clearing activity which was 82 per cent of the normal.

These results seem to suggest that there is an active principle in the pancreas which might be responsible for the production of lipemia clearing factor in the normal animal. Further investigation is in progress to elucidate the nature of this active principle.

2:55 Discussion

3:00

37. Human Studies with the Lipid Mobilization Factor

I. J. Greenblatt. From the Messinger Research Laboratories, Brooklyn, N. Y.

Seifter has recently reported a presumed peptide capable of inducing marked lipemia in fasted laboratory animals, when injected intravenously. Material obtained from Seifter (Wy-991) injected at levels from 1 mg. to 60 mg./Kg. in humans showed the following in 21 patients:

Two patients given 10 mg./Kg., (30 mg. of L. M. factor/ml.), showed no lipemia, little change in fatty acids, no significant change in cholesterol, and a slight fall in lipoproteins of the S_f 0–400 class.

Five patients given 20 mg./Kg. showed slight lipemia in 1, and a small rise in fatty acids and a fall in lipoproteins of the S_f 0–400 class.

Eight patients given 30 mg./Kg. showed slight lipemia in 1, insignificant changes in fatty acids and cholesterol and about a 10 per cent fall in all of the

4 lipoprotein classes (S_f 0–12, 12–20, 20–100, 100–400).

In patients treated with L. M. factor diluted by an equal volume of saline very little change was observed, except that the S_f 0–20 lipoproteins rose; no lipemia was noted. At a level of 40 and 60 mg./Kg., severe reactions were encountered, with accompanying chest pain, syncope, and tachycardia, in 2 patients.

3:10 Discussion

3:15

38. Spaced Fat Feeding: A Regime of Management for Familial Hyperlipemia

Chas. F. Wilkinson, Jr. From the Department of Medicine of New York University Post-Graduate Medical School, New York, N. Y.

By proper spacing of the amount of fat consumed during a 24-hour period, it is possible to maintain normal levels of cholesterol, phospholipids and total fatty acids in familial hyperlipemia after blood levels have been reduced to normal by rigid fat restriction for a period of 30 days. By visual inspection of serum or plasma, we believe that approximately 75 per cent of early heterozygous familial hyperlipemics can be picked up without the use of a fat tolerance test.

This regime has the following advantages: (1) It is easy to follow from the patient's point of view; (2) it does not restrict the patient's social intercourse by making him appear different because of his diet; (3) it does not rule out "snacks;" (4) unavoidable departures from the regime can easily be corrected.

A working hypothesis of the genetic mode of transmission and the metabolic defect in familial hyperlipemia will be presented. This includes the concept that the heterozygous abnormal is far from infrequent, though not as dramatic clinically as the homozygous abnormal.

Since there appears to be a tendency for older people to clear fat less well than younger people, this regime may also be applicable as a prophylactic measure in an aging population.

3:25 Discussion

3:30

39. Zone Electrophoretic Studies on Serum Lipids in the Elderly

Philip G. Ackermann, Gelson Toro and William B. Kountz. From the Division of Gerontology, Washington University School of Medicine and St. Louis Chronic Hospital, St. Louis, Mo.

The serum lipids have been studied in more than 350 elderly subjects by use of zone electrophoresis on a starch medium. Measurements of the cholesterol and lipid phosphorus showed the presence of 3 fractions, each with a relatively constant cholesterol-phosphorus ratio. It was found that measurement of the cholesterol distribution alone in the fractions was satisfactory for comparative purposes. Differences in the cholesterol distribution between the fractions were found in comparing men and women with the same total cholesterol level, in that the percentage of cholesterol in the beta fraction was higher in the men. Serial determinations on subjects with cardiovascular disease or on treatment with hormones showed some correlation between changes in the cholesterol distribution pattern and the clinical status. A number of subjects, almost all of whom were men, showed an abnormal distribution pattern with a large alpha-2 fraction. In some instances this abnormal pattern persisted over a period of several years.

3:40 Discussion

3:45

40. Serum Protein, Lipoprotein, and Glycoprotein Patterns as a Diagnostic Aid in Suspected Myocardial Infarction

O. J. Pollak. From Dover, Del.

Filter paper electrophoretic patterns (elpherograms) of proteins, lipoproteins and glycoproteins were obtained from the sera of 20 patients with uncomplicated angina pectoris and the patterns compared with those from 32 patients with angina pectoris and myocardial infarction.

Deviations in patterns of patients with angina pectoris but without infarction were insufficient to allow their differentiation from healthy persons. Alterations in patterns of patients with angina pectoris complicated by myocardial infarction were sufficiently characteristic to single out these patients. Prominent deviations from the norm, in patients with recent myocardial infarction, were an increase in serum α_2-glycoprotein, increase in α_2-globulin, increase in total globulin, decrease in albumin, and decline in total cholesterol.

Though deviations from normal patterns are not pathognomonic for myocardial infarction, electrophoretic partition of proteins, protein-bound lipids, and protein-bound carbohydrates, together with assay of serum protein and cholesterol, is of distinct value in differential diagnosis between angina pectoris with or without myocardial infarction.

3:55 Discussion

4:00

41. Influence of Nicotinic Acid on Cholesterol Metabolism

*Rudolf Altschul. From the Department of Anatomy of the University of Saskatchewan, Saskatoon, Canada.**

In healthy young persons and in many adults with various diseases, oral administration of nicotinic

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acid in large doses is followed after a short time by a decrease of serum cholesterol (Altschul, Hoffer and Stephen, Arch. Biochem. **54,** 558, 1955). Similar results were obtained in tests with rabbits. 1. Nicotinic acid was given in capsules (3 × 0.045 Gm., 3 × 0.09 Gm. or 3 × 0.18 Gm. respectively) over 24 hours to rabbits with normal serum cholesterol or with cholesterol levels which had been raised artificially. After this period, the cholesterol was lower in 20 out of 24 tests by 14 per cent (S.D. ± 20, S.E. ± 4.1). 2. Following single subcutaneous injections of either 0.045 Gm., 0.09 Gm. or 0.15 Gm. of nicotinic acid, the serum cholesterol was lower in 18 out of 22 tests by a mean of 10.9 per cent (S.D. ± 11.5, S.E. ± 2.45). Thus the decrease of serum cholesterol after oral or parenteral administration of nicotinic acid is highly significant. 3. Over periods of 90 days, 17 rabbits received daily 0.3 Gm. cholesterol in capsules and, in addition, capsules containing 0.45 Gm. nicotinic acid (15 animals) or 0.36 Gm. (2 animals), also daily. The serum cholesterol at the ninetieth day averaged 229 mg. per cent, well below the mean serum cholesterol level (540 mg. per cent) of rabbits which had received the same doses of cholesterol, for the same periods, but no nicotinic acid. Macroscopic and microscopic inspection of tissues of these rabbits showed no "cholesterol damage" in 9 cases, slight damage in 6 and intense damage in 2 animals, indicating inhibition or mitigation of atherosclerosis in 15 out of 17 cases.

4:10 Discussion

4:15

42. The Effect of Large Doses of Nicotinic Acid on the Plasma and Serum Lipids of Human Beings with Hypercholesterolemia

William B. Parsons, Jr., Richard W. P. Achor, Kenneth G. Berge, Bernard F. McKenzie and Nelson W. Barker. From the Mayo Foundation and Sections of Medicine and Biochemistry of the Mayo Clinic and Mayo Foundation, a part of the Graduate School of the University of Minnesota, Rochester, Minn.

Since Altschul and associates found that the concentration of serum cholesterol in normal and hypercholesterolemic individuals was reduced during a 24-hour period by oral administration of 1 to 4 Gm. of nicotinic acid, the present study was undertaken to determine the effect of similar large doses of this drug during prolonged periods. Thirteen patients were treated for 12 weeks or longer. The initial dose of nicotinic acid was 3 Gm./day divided into either 4 or 6 doses. In some the dose was reduced to 1.5 Gm./day after several weeks, and in others it was increased to 4.5 or 6 Gm./day. Several samples of blood were tested before treatment was started and subsequent tests were made at weekly intervals for the first 4 weeks of treatment and at biweekly intervals thereafter. Cholesterol and total lipids were determined on each plasma sample; the cholesterol content of the α-globulin and β-globulin fractions of the serum was determined on each sample by the method of Zak. During the period of treatment the values for plasma cholesterol decreased significantly in 9 of the 13 patients. The ratio of β-globulin cholesterol to α-globulin cholesterol decreased in 11 of the 13 patients and the concentration of total lipids in the plasma decreased slightly. In none of the patients did the concentration of plasma cholesterol or total lipids exceed the control values during the period of treatment. Side reactions consisting of flushing and pruritus were no greater than those seen after administration of 50 to 100 mg. of nicotinic acid, and these reactions tended to diminish and usually disappeared after the first few days of treatment. Urticaria, nausea and vomiting were observed in 2 patients but subsided when the drug was withheld temporarily and did not recur when administration was resumed. Nausea and vomiting occurred in 2 other patients which necessitated abandoning the treatment. No evidence of impairment of hepatic function or other untoward complications was encountered during administration of the drug.

4:25 Discussion

TO BE READ BY TITLE

4:30

43. A Practical Method for Reducing Plasma Cholesterol in Man

Henry A. Schroeder. From the Hypertension Division of the Department of Internal Medicine, Washington University School of Medicine, St. Louis, Mo.

On the assumption that the high levels of plasma cholesterol found in European and American individuals as compared to those of more primitive people are the result of the food habits of western civilization, a regimen was devised to include several cholesterolytic influences and applied to 20 hypertensive and atherosclerotic patients. Plasma cholesterol was measured biweekly by the method of Saifer and Kammerer.

1. Calcium disodium ethylenediamine tetraacetate (CaEDTA) 1.0 Gm./day, given orally. Previous studies in 11 patients have shown declines of plasma cholesterol of from 36 to 154 mg./100 ml. (mean 60.9) in 9 and no significant changes in 2, in 4 to 44 weeks, when this chelating agent was given orally.

2. Some reduction of animal fat in diet, by elimination of milk fats and pork products.

3. The use of vegetable oils containing linolenic acid for cooking and salad dressings, with a daily intake advised. Soy bean oil (8 per cent linolenate) was preferred to corn oil (0.5 per cent linolenate).

From the work of others (Kinsell and associates, Ahrens and co-workers, Beveridge and associates) 1 common denominator of cholesterol-lowering fats, as compared to cholesterol-raising fats, appears to lie in the presence of linolenic acid.

4. Pyridoxine hydrochloride, 10 mg./day. While this vitamin has not been shown to be cholesterolytic, indirect evidence has indicated its role in desaturation of fatty acids, and its absence has caused subintimal lesions resembling those of early atherosclerosis in monkeys (Rinehart and Greenberg). On this regimen, a mean fall of plasma cholesterol from 258 to 183 mg./100 ml. occurred in 2 months, with a rise to 206 mg./100 ml. in 4 months. Fluctuations to levels of 112 to 160 mg. occurred in half; 3 failed to respond at all. Symptomatic improvement was evident in 5 of 6 with ischemic manifestations and slight regression of xanthomata in 2. No evidence of hepatic damage was observed. The method is practical and the diet not too severely restrictive.

44. Intravenous Cholesterol Tolerance Test

R. F. Ackerman and J. W. Ragsdale, Jr. From the Division of Preventive Medicine of the University of Tennessee, Memphis, Tenn.

A concentrated aqueous cholesterol suspension suitable for intravenous administration has been developed. Using 3 to 5 per cent concentrations of this suspension, 6 fasting, anesthetized dogs were injected with 2 Gm. of cholesterol. Within 10 min. the serum cholesterol rose 2 to 3 times the control value. Within 2 to 4 hours, the cholesterol level dropped to 1½ or less times the control value. Then there was a slower return to the control level, which was reached in 6 to 18 hours. Curves for the 6 dogs were consistent within limits of biologic variation. Plasma turbidity values paralleled cholesterol levels to a remarkable degree. No toxic manifestations were observed; some animals were kept alive for several weeks after the administration of the cholesterol suspension and remained entirely well, others were autopsied at the end of 12 or 18 hours and no gross or microscopic lesions were found in heart, lung, aorta, liver, spleen, or kidney. Preliminary data on intravenous cholesterol tolerance in "normal" and atherosclerotic humans indicates that similar type curves result. Cholesterol loading might reveal a metabolic defect in those individuals that are developing atherosclerosis prematurely, or be employed as a diagnostic or experimental procedure to study drugs, etc., which might influence atherogenesis.

45. Serum Lipoproteins in Peripheral Arteriosclerosis

Norman H. Azen, Lena L. Lewis, and Victor G. deWolfe. From the Department of Medicine and the Research Division, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Serum lipoprotein concentrations ($-S_{1.21}$, Green, Lewis and Page modification of Gofman's procedure) were measured in 84 nondiabetic patients with peripheral or aortic atherosclerosis demonstrated by angiograms, concurrently with determinations of serum cholesterol. The method used determines high-density lipoproteins ($-S$ 1–10) and those of low density ($-S$, 70–400, 40–70, 25–40), corresponding approximately to α and β-lipoproteins.

The averages of the group indicate increases in concentrations of serum cholesterol and low-density lipoproteins with a decrease in high-density lipoprotein content. Definite increases in low-density lipoprotein content were found in 21 (25 per cent) and probable increases in 15 (18 per cent) with normal values in 48 (57 per cent). Incidences of increased serum low-density lipoprotein concentrations were nearly the same in patients with extensive as in those with segmental atherosclerosis. Incidences and mean averages of abnormal lipoprotein concentrations were greater in patients with occlusion of the aorta or iliac arteries than in those with occlusion of the femoral arteries.

In comparison with a normal population of the same age, these patients show an increased incidence of high concentrations of low-density lipoproteins, with concurrent increases in serum cholesterol and decreases in high-density lipoprotein concentrations. However, these abnormalities are demonstrable in less than half of the patients and show no association with the extent of the arterial disease. The observations support the view that abnormalities of serum lipoprotein may participate in the pathogenesis of arteriosclerosis, but indicate also that other, unrecognized factors are of equal or greater significance.

46. A Standardized In Vitro Method for Evaluation of Clearing Factor Response in Man: Its Application to an Agewise Study

Saul P. Baker. From the Gerontology Branch, National Heart Institute, National Institutes of Health, Bethesda, and the Baltimore City Hospitals, Baltimore, Md.

Studies of heparin-activated clearing factor response in man have utilized a wide range of heparin dosage, different substrates and different technics. In order to define more precisely the individual response of this heparin-activated lipase, a minimal heparin stimulus, 3 mg. (Upjohn), fasting subjects, and a standard cocoanut oil emulsion (Ediol, Schenley) have been employed in the development of a standardized in vitro assay method.

Postheparin plasma was mixed with fat emulsion and incubated at 30 ± 1 C. for 1 hour. Optical densities were read every 5 min. in a Beckman Model DU spectrophotometer at 6500 Å. A graph of optical density versus time was then plotted. To this plot, a straight line was visually fitted. The slope of this line, k, (decrease in optical density per hour) represented the rate of clearing of postheparin plasma.

Clearing factor concentration was shown to be proportional to k by comparing calculated and actual k's for 57 mixtures of postheparin plasmas ($r = 0.95$). Reliability of the method was determined by duplicate runs on 52 postheparin plasmas. The standard error of the mean k was ± 0.06. Biological variability was determined by repeat runs at least 1 week apart on 34 different subjects. The standard error of the mean k was ± 0.13.

A group of 84 men, ranging from 21 to 93 years of age, was selected from the population of the Infirmary Division (Old Peoples Home) of the Baltimore City Hospitals and from convalescent patients shortly before discharge from the acute wards. All subjects were afebrile, free from evident acute infection, on regular diet and taking fluids ad lib for at least 1 week prior to test. The mean k of this population was 0.74, ($\sigma_d = 0.29$). The mean age was 61.3 ($\sigma_d = 17.8$). No significant regression of k on age was found in this population. Three subjects in the 20 to 59 age group were found to have k's greater than 1.10; all of these men were chronic alcoholics.

47. Effects of Cholesterol Feeding in the Shell Parakeet (Melopsittacus undulatus)

Thomas R. Blohm, Leonard J. Lerner, Takashi Kariya and Marie E. Winje. From the Departments of Biochemistry and Endocrinology-Pathology, Research Laboratories of the Wm. S. Merrell Company, Cincinnati, Ohio.

Young (8-week) male and female parakeets (budgerigars) were fed a normal seed diet with or without added cholesterol and cottonseed oil. One per cent cholesterol for 12 to 15 weeks (with 5 per cent cottonseed oil for the last 7 to 10 weeks) produced extreme hypercholesteremia, hyperphospholipemia and isolated atheromata in the elastic aorta. No lesions were found in the abdominal aorta or in the coronary arteries.

The degree of hypercholesterolemia corresponded to that attainable in the rabbit or chicken, but the amount of induced atherosclerosis was much less.

Normal parakeets exhibit blood lipid levels which are higher than those occurring in mammalian species and chickens, and are quite variable. Administration of estradiol benzoate, 1 mg./30 Gm. bird, 3 times a week for 12 weeks approximately doubled plasma total cholesterol and phospholipid levels.

48. Variations in Capacity of Animals to Handle Exogenously Fed Cholesterol

William S. Collens. From the Medical Services of the Maimonides Hospital and the State University of New York, College of Medicine, Brooklyn, N. Y.

Studies in overloading 50 rabbits with exogenously fed cholesterol reveal specific variations in individual ability to handle this cholesterol. While some rabbits showed a rapid response to feeding 1 Gm. a day with a rise in serum cholesterol, others showed no effect upon their serum levels at all. The animals that responded showed, in most cases, a progressive rise in their levels, reaching a peak in approximately 12 weeks, after which the concentration of serum cholesterol receded over a period of another 10 to 12 weeks, finally reaching their original normal resting levels. These animals would again respond when the cholesterol intake was increased to 2 Gm. The response curve was similar to that which followed the original 1 Gm. feeding. Some of the animals which could tolerate 1 Gm., showed a response curve by a rise in serum cholesterol when the dose was doubled. This response too was characterized by a slow and progressive rise, reaching its peak in 6 to 10 weeks, and then slowly receding to normal. Other animals appeared to tolerate 2 Gm. feedings daily and did not show any serum cholesterol elevation until the dose was increased to 3 Gm.

It would appear that feeding cholesterol evokes a homeostatic mechanism in the rabbit, which helps the animal to handle the overload. Comparable studies in the dog, which is a carnivore, indicate that he is able to handle overloads in cholesterol feeding to an inordinate degree. Hypercholesterolemic response to overloading in the dog becomes manifest when 100 Gm./day of cholesterol is fed.

Investigations related to absorption of cholesterol from the gastrointestinal tract, degradation and final fate of this material are in progress. A dose relationship to alterations in arterial walls is also being investigated, as well as the implications in human disease.

49. Moving Boundary Electrophoresis of Lipoproteins

Harold B. Eiber, Isidore Danishefsky and James Sang. From the Gilman Laboratory of the New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.

The low density lipoproteins obtained by ultracentrifugation of serum in a solution density of 1.063 were studied by means of moving boundary electrophoresis. At pH 8.6, in veronal buffer, ionic strength 0.1, these lipoproteins give a clear electrophoretic pattern showing concentration dependence but no change in mobility. Serum from which this fraction has been removed shows primarily a decrease in β-globulin, while addition of this material to normal serum shows an increase in β-globulin.

Addition of excess low density lipoprotein to serum does not cause any major disturbance or alteration of the general pattern and the individual peaks are easily discernible. It is therefore inferred that the pattern disturbance seen with lipemic sera is not due to these lipoproteins but to some other substance.

Although lipoproteins may produce various boundary artifacts in free electrophoresis, this technic can be used to study changes in lipoproteins during

clinical and metabolic studies. The effect of heparin and other drugs can be observed in this manner.

Thus, for clinical characterization, lipoproteins can be isolated by ultracentrifugal flotation and their characteristics and differences studied electrophoretically. This method can be employed to study various alterations and metabolic transformations involving lipoproteins.

50. Studies of Circulating Human Endogenous Lipoprotein Lipase: Heparin Lipemia Clearing Factor

Hyman Engelberg. From Beverly Hills, Calif.

Evidence has recently been presented of the existence of lipemia clearing factor in the blood of some individuals without the prior injection of heparin, (Am. J. Physiol. **181:** 309, 1955). The activity was usually found only in plasma and had inhibition characteristics similar to the postheparin clearing factor. However, in the initial studies decreases in the optical density of a fat substrate were followed and the hydrolytic nature of the reaction was not proven. More recent studies have confirmed the release of unesterified fatty acids from fat substrates in vitro by endogenous clearing factor, thus establishing that hydrolysis of neutral fat occurs in the blood stream.

In other investigations the quantitative role of endogenous lipemia clearing factor (lipoprotein lipase) in the removal of postalimentary lipemia from the bloodstream was investigated in those subjects previously found to have high levels of activity. Postlipemic plasma was incubated in vitro at 37 C., and neutral fat fatty acid was determined. The release of unesterified fatty acids (free fatty acids) was measured after 15, 30, 45, 60 and 120 min. incubation. The lipolytic activity was variable in the same patient at different times. In several instances lipolysis of the total available triglyceride occurred in vitro in ½ to 1 hour with as much as 2.7 mEq./L. of unesterified fatty acid released in ½ hour.

These findings afford further evidence of the physiologic role of plasma lipoprotein lipase in lipoprotein transformations. The reaction demonstrated in vitro in some subjects is quantitatively sufficient to account for the hydrolysis and removal of postalimentary lipemia from the bloodstream.

51. Aorta Atherogenesis in Different Strains of Hybrid Cockerels

D. Friedman, P. Johnson, R. Pick, J. Stamler and L. N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Based on empiric observations in different groups of Hy-Line cockerels, it was deemed necessary to explore systematically strain differences in susceptibility to cholesterol-induced atherosclerosis. Five strains were studied: White Rocks, Leghorns, Hy-Line-900 Series (cross of inbred lines of light breed), Hy-Line-100 Series (cross of inbred lines of light male and heavy female breed) and Hy-Line-800 Series (cross of inbred lines of dark breed). All groups were fed a chick starter mash supplemented with 2 per cent cholesterol plus 5 per cent cottonseed oil. After 5 weeks on this atherogenic regimen, White Rocks and Hy-Line-800 Series exhibited no gross lesions in the thoracic aorta, in contrast to the other groups. With more prolonged feeding of the atherogenic diet, these 2 groups manifested moderate atherogenesis, significantly less in incidence and severity than the other 3 strains. The Hy-Line-900 Series was apparently the most susceptible. These differences in atherogenic response could not be correlated with patterns of hypercholesterolemia.

52. Age Related Properties of Postmortem Aortas from Swine

Howard Gottlieb. From the Bjorksten Research Foundation, Madison, Wis.

The striking similarities between postmortem human and swine aortas have prompted us to utilize the porcine aorta as an experimental tissue for biophysical study. The dimensional characteristics of adventitia-free aortas exhibit increases in total diameter, wall thickness, lumen area and mass per unit length almost in proportion to the total body weight.

Elastomeric properties of nonsclerosed adventitia-free aortic segments show an apparent loss of elasticity with increasing age. However, the modulus of elasticity shows no age-related alterations, but individual aortas from different animals of the same age show considerable variation. The thoracic segment appears to have a greater modulus than the abdominal segment from the same aorta. Longitudinal loading hysteresis cycles indicate no loss of damping capacity with age.

Whole aortic segments undergo immediate dimensional change upon extirpation. The whole aortic segment has age-related elastic properties different from the adventitia-free aortic segment. Some of the elastic properties of the adventitia will be described relative to pulsatile hemodynamic distortion and histogenesis of arteriosclerosis.

53. Effect of Insulin on the Lipfanogen-Antilipfanogen Balance in Diabetes

Charles R. Harmison and Henry S. Simms. From Columbia University, New York, N. Y.

Diabetic patients admitted to the hospital in a state of acidosis are being studied before and after the administration of insulin. Preliminary results on the first 5 patients who were studied showed that

before insulin treatment the free antilipfanogen in the serum was abnormally low (3.0 to 6.6 units) and the fat-depositing free lipfanogens were correspondingly high (up to 36.0 units).

Twenty-four hours after injections of insulin were started there was, in every case, a marked rise in the antilipfanogen. In four cases this ranged from a 2.4 fold to a 10 fold increase in this protective agent. At the same time the free lipfanogens dropped to values 0.2 to 0.6 of the previous levels.

The lipfanogen and antilipfanogen values were determined by the fat-depositing action of the serum in tissue cultures under standard conditions

54. The Effect of a Test Meal of Animal Fat on the Lipids and Lipoproteins of Human Serum, and on Some Aspects of Liver Function in Normal Individuals and in Those with Coronary Atherosclerosis

Louis Horlick. From the Departments of Biochemistry and Medicine, University of Saskatchewan Medical School, Saskatoon, Sask., Canada.

Various aspects of lipid metabolism were studied in the fasting state, and 2, 4 and 6 hours after a test meal of 1.0 to 1.5 Gm. of butter fat/Kg. body weight. In a manner analogous to the glucose tolerance test, it was hoped that the lipid load would uncover hidden defects in the metabolism of the lipids.

1. The control levels of serum cholesterol, phospholipid, fatty acids, and serum turbidity were all higher in the group with coronary disease. The per cent of cholesterol in the α-lipoprotein fraction was lower in this group than in the normals.

2. The administration of the high fat test meal failed to result in any change in the cholesterol, but there was a modest rise in the phospholipids and a fall in the c/p molar ratio which was statistically significant in the coronary group. There was a marked rise in the total fatty acids and serum turbidity in both groups, with a greater increment in the coronary group. There was no change in the percentage of cholesterol in the α- and β-lipoproteins.

3. The administration of a diet in which 60 per cent of the calories were supplied as animal fat for a period of 3 weeks failed to alter the response to repeated test meals in 3 normal subjects.

4. The serum proteins rose following the test meal with high values at 2 and 4 hours, and returned to base line at 6 hours. The increase was statistically significant in the normal group. Electrophoresis of the proteins on paper failed to reveal a consistent increase in any fraction.

5. Thymol turbidity determinations carried out after removal of the chylomicrons by centrifugation showed higher values for the coronary group, but there was no significant change following the high fat meal.

6. Serum lipoprotein stability was tested by the "lecithinase test," and as previously reported by us, was found to be reduced in the coronary group. The high fat meal did not influence the stability in either group.

55. The Effect of Low Fat Diet and Sitosterol on the Serum Lipids of Patients with Coronary and Peripheral Arterial Diseases

Peter T. Kuo and Claude R. Joyner, Jr. From the Robinette Foundation, Medical Clinics, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Sixteen patients with coronary and/or peripheral arterial disease were put on a diet of 20 Gm./day of fat for periods of 2 to 6 months. Ten of the 16 patients who cooperated showed a gradual progressive lowering of their serum cholesterol and total esterified fatty acid levels ranging from 16.6 to 28.5 per cent of their initial control levels. The serum lipids of these 10 patients continued to fall following the administration of 27 to 45 Gm./day of sitosterol (Cytellin, Lilly) in addition to the low fat diet for periods of 2 to 18 months. This secondary fall in blood lipids ranged from 7 to 18 per cent of the premedication blood lipid levels. However, administration of a placebo in place of the sitosterol for 4 to 6 weeks to these 10 patients after their blood lipid levels had been lowered to their respective minimums by diet and sitosterol did not result in a significant increase in their serum lipids. The other 6 patients in the treated series who made intermittent efforts to follow the dietary restrictions showed no consistent change in blood lipid pattern before and after sitosterol therapy.

Five patients in the "control" group received a placebo together with a diet estimated to contain 60 to 80 Gm./day of fat showed no significant change in their blood lipid levels for periods from 3 to 18 months.

56. Toxicity of β-Aminopropionitrile for Turkey Poults

J. J. Lalich, B. D. Barnett, H. R. Bird, and F. M. Strong. From the Department of Pathology of the University of Wisconsin, Madison, Wis.

Day-old Broad Breasted Bronze poults received varying levels of β-aminopropionitrile hydrochloride (BAPN-HCl) in a practical diet. This compound, the toxic agent of *Lathyrus odoratus* seeds, causes skeletal deformities and aortic rupture within 4 to 7 weeks in rats when fed at a 0.25 per cent concentration in the diet. In turkey poults, however, concentrations of 0.125 and 0.25 per cent produce leg paralysis with degeneration of anterior motor neurons and multiple hemorrhages in less than 1 week. Pulmonary, pericardial or muscular hemorrhages were

observed in 4 of 12 birds fed 0.06 per cent BAPN-HCl in the diet. Concentrations of 0.03, 0.04 and 0.06 per cent BAPN-HCl produced less paralysis of toes and legs; however, 10 of 37 died of abdominal aortic rupture. In contrast to the observations in test poults weight gains were greater and no abnormalities were observed in 42 control birds. In the aortas of poults fed BAPN-HCl, it was observed that medial edema and hyaline degeneration of the elastic fibers invariably precedes the dissecting medial hemorrhage and aortic rupture. The gross and microscopic changes in the arteries of the turkey poults will be compared with the alterations which occur in rats to illustrate species susceptibility and differences in arterial response to BAPN-HCl feeding.

57. Thromboangiitis Obliterans and Atherosclerosis: Part I

Irving Leinwand, A. Wilbur Duryee and Maurice N. Richter. From the Departments of Medicine and Pathology, New York University Post-Graduate Medical School and the Medical Service, University Hospital, New York, N. Y.

The records of all patients admitted to the University Hospital during the past 16 years with a diagnosis of thromboangiitis obliterans (TAO), were reviewed. Out of 80 patients in whom this diagnosis was made, 3 definite, 17 clinically probable and 7 clinically possible cases were secured. Of the remaining 47 patients eliminated as having TAO, 40 appeared to be cases of atherosclerosis. Of 6 major amputation cases, only one had TAO on pathologic examination. In the recent investigations of the problem of atherosclerosis, attention has been focused on coronary atherosclerosis with some investigators inclined to differentiate the lesions in the heart from those in the extremities or to ignore the latter entirely. The continual reference to arteriosclerosis of the lower extremities without differentiation as to type is responsible for the large per cent of errors in diagnosis, since evidence of occlusive arterial disease in a young male in the absence of calcification was considered ipso facto evidence of TAO.

TAO is undoubtedly a more uncommon disease than has generally been accepted. From our observations, we think it may be doubtful that the diagnosis of this arterial disease should be made in the absence of venous involvement. Ischemia, with or without gangrene, produced by reduction of blood flow due to narrowing of the lumen of the artery by atherosclerosis, with or without thrombosis, is probably more common in young males than thromboangiitis obliterans.

58. Serum Lipid Fractionations in Selected "Atherosclerotic" and "Normal" Males

J. A. Little, H. M. Shanoff, R. W. Van der Flier and H. E. Rykert.† From the Sunnybrook Veterans' Affairs Hospital, Toronto, Canada.

Male veterans with proven coronary atherosclerosis (approximately 25 in each decade from the fourth to the eighth inclusive) were carefully selected and studied along with a matched control group without evidence of clinical atherosclerosis. Both groups were free of hypertension or diseases commonly associated with secondary hypercholesterolemia. The 2 groups were compared with regard to family history, dietary history, body build, obesity, serum lipid fractions and numerous relevant clinical data.

Decade	Total cholesterol		S_f 0-400	
	Normal	Coronary	Normal	Coronary
4	205 ± 29	286 ± 53	457 ± 93	704 ± 181
5	215 ± 38	263 ± 33	470 ± 105	665 ± 140
6	206 ± 30	250 ± 47	445 ± 84	569 ± 138
7	216 ± 37	231 ± 36	445 ± 153	473 ± 115
8	213 ± 38	243 ± 53	452 ± 117	487 ± 148

In the control group, total serum cholesterol (Schoenheimer-Sperry), phospholipid (Zilversmit and Davis) and standard S_f 0-400 lipoproteins did not vary with age, (see table). By comparison, all of these serum lipid fractions were present in notably higher concentrations in the coronary group, most significantly so in the younger decades. The relative differences in the concentrations of the different lipid fractions between the control and coronary groups will be discussed. By arbitrarily using a total serum cholesterol level of 241 mg. per cent, more than 80 per cent of the men in the fourth decade control and coronary groups are correctly separated. The relationship of the serum lipids to dietary factors, body build, obesity, corneal arcus, aortic calcification and other clinical data will be presented.

59. Lipid Deposits in the Aortic Cusp of the Mitral Valve. II. Microscopic Features of the Leaflet and of the Fat Distribution

J. F. McManus. From the Department of Pathology of the University of Alabama Medical Center, Birmingham, Ala.

The author, with Montgomery, has previously described the fact that grossly recognizable deposits of lipid in the aortic cusp of the mitral valve have had, in a series of 300 cases, the occurrence which is very much like that of atherosclerosis of the aorta, i.e., less common in the first decade of life, more

† Deceased.

common in the older age groups. This lipid deposit which is present in the aortic cusp of the mitral valve in so many instances is colorable with Sudan dyes and may show the reactions of cholesterol. The data reported in the present paper show that the cusp has a structure which is considerably different from the ordinary arterial wall and that the fat is deposited not only into cells but into ground substance. These latter features distinguish the process from atherosclerosis, suggesting that the lipid deposits in the aortic cusp of the mitral valve permit an analysis of some of the factors controlling atherosclerosis.

60. Chronic Sodium Chloride Toxicity: The Protective Effect of Added Potassium Chloride

George R. Meneely, William J. Darby, Janet Lemley-Stone, Robert G. Tucker, Con O. T. Ball and John B. Youmans. From the Radioisotope Service, Thayer Veterans Administration Hospital and the Departments of Medicine, Biochemistry and Preventive Medicine and Public Health, Vanderbilt University School of Medicine, Nashville, Tenn.

Increased sodium chloride fed to rats in a purified diet leads to decreased growth, hypertension, hypercholesterolemia, edema, renal and cardiac failure, increased sodium space, abnormal electrocardiograms, accelerated mortality and widespread arteriolosclerosis proportional to salt intake. We suggested in the fall of 1952 that potassium might alter the effects of increased sodium chloride. Possible dietary interrelation of sodium and potassium has been hypothesized since 1843 when chemical analysis revealed the important difference between the sodium potassium ratio of herbivorous and carnivorous diets. Experiments to test this hypothesis were started in 1953. The first of these is now complete. The protective action of potassium chloride added to diets containing toxic levels of sodium chloride is indicated by the increased survival rates of high NaCl-high KCl fed rats and the apparent reduction in hypertension and its effects. Survival of rats eating 8.4 per cent NaCl fell to 50 per cent in 16 months at which time among rats eating 8.4 per cent NaCl plus 4.7 per cent KCl survival was 75 per cent and it did not fall to 50 per cent until 8 months later. Among rats eating 5.6 per cent NaCl the protective effect of added KCl was even more impressive. Survival of rats eating 5.6 per cent NaCl fell to 50 per cent in 20 months at which time among rats eating 5.6 per cent NaCl plus 2.9 per cent KCl survival was 95 per cent and it did not fall to 50 per cent until 7 months later. Survival of these rats actually exceeded that of "controls" receiving from 0.15 to 1.1 per cent NaCl. Important differences in total body sodium determined with the radioactive isotope were found. At levels above 5.6 per cent of dietary NaCl total body sodium was increased substantially. When KCl was added to diets high in NaCl total body sodium remained normal.

61. The Lipids, Nitrogen Fractions, and Polysaccharides of Canine Aortae and the Alterations Induced by the Administration of Allylamine

Leonard N. Norcia, I. Ernest Gonzalez, M. R. Shetlar, Joanna Peter and Robert H. Furman. From the Cardiovascular Section of the Oklahoma Medical Research Foundation, the Departments of Medicine and Biochemistry of the University of Oklahoma School of Medicine and the Research Laboratory of the Veterans Administration Hospital, Oklahoma City, Okla.

The influence of allylamine-induced injury on the concentration of a number of constituents of canine aortic tissue has been studied. The arch, thoracic, and abdominal aortae of 46 apparently healthy, young, middle-aged and old mongrel dogs of both sexes were analyzed chemically and studied histochemically for several lipid, nitrogen, and polysaccharide components. The same measurements and studies were made on a similar group of 36 dogs treated intravenously with allylamine.

Average values (mg./Gm. dry weight tissue) for lipid and nitrogen fractions with standard deviations for all control animals are shown in the table.

	Arch	Thoracic	Abdominal
Cholesterol	5.78 ±0.92	5.25 ±0.84	3.80 ±0.91
Lipid P	0.876±0.135	0.757±0.099	0.571±0.101
Mg. cholesterol/Mg. lipid P	6.53 ±1.14	6.72 ±1.37	6.71 ±1.39
Total nitrogen	160.0±9.0	162.4±8.6	165.1±8.6
Alkali-soluble N	70.4±7.7	64.4±8.6	55.1±13.2
Alkali-insoluble N (collagen plus elastin)	89.6±10.4	98.0±11.0	110.0±15.3

Concentration gradients along the length of the aorta evident in the above data for cholesterol, lipid P, alkali-soluble nitrogen, and alkali-insoluble nitrogen are statistically highly significant ($p > 0.001$). A number of significant differences were found among the age-sex groups; the most striking differences were between cholesterol levels and cholesterol/lipoprotein ratios for young and old males. Following allylamine administration small but significant increases in cholesterol and alkali-soluble nitrogen were observed.

Histochemical studies, corroborated by chemical analyses, show a concentration gradient of both acid and neutral polysaccharides—highest in the arch and lowest in the abdominal aorta. Minor changes in polysaccharides following allylamine administration were revealed histochemically and/or chemically.

Acetal phosphatides were abundant histochemically and followed the gradient for lipid P

noted above. Acetal phosphatides were observed in juxtaposition to elastic fibers, while other lipids were mostly intracellular.

Cell population studies and tissue potassium levels along the aorta do not appear to correlate with the gradients observed.

62. Fat Ingestion and Serum Lipoproteins: Studies by Starch Electrophoresis in Normals and in Persons with Idiopathic Hyperlipemia

Fiorenzo Paronetto, Chun-I Wang and David Adlersberg. From the Departments of Medicine and Chemistry, Mount Sinai Hospital, New York, N. Y.

Using starch electrophoresis, idiopathic hyperlipemia was found to be characterized by marked elevation of both cholesterol and phospholipid content in the α_2-lipoprotein fraction, whereas idiopathic hypercholesteremia exhibited a considerable elevation of these factors in the β-lipoprotein fraction (Clin. Res. Proc. **4:** 91, 1956.).

In continuation of this study 2 patients with idiopathic hyperlipemia were treated with low fat diets for 1 week and 3 months, respectively. In 1 patient, a marked reduction of serum lactescence occurred with a decrease of total lipids from 3000 to 2100 mg. per cent. These changes were associated with a decrease in the cholesterol from 55 to 4.6 per cent and phospholipid from 63.5 to 12.9 per cent in the α_2-lipoprotein. There was a marked increase of these factors in the β-lipoprotein (cholesterol from 40.5 to 92.6 per cent, phospholipid from 27.8 to 80.5 per cent) without any significant changes in the α_1-lipoprotein. The second patient showed delactescence of serum, a drop of total lipids from 2300 to 1220 mg. per cent and changes in the lipoprotein fractions similar to those observed in the first patient. Thus the use of a low fat diet in idiopathic hyperlipemia affected serum total lipids and triglycerides, lowered the concentration of both cholesterol and phospholipid in the α_2-lipoproteins and raised the concentration of these factors in the β-lipoprotein.

The effect of a fat loading test (2 Gm./Kg. of butter fat) was studied in two normal controls. At the height of alimentary lipemia there was a decided increase in cholesterol (3.4 to 13.5 per cent) and in phospholipid (1.0 to 16.5 per cent) in the α_2-lipoprotein fraction with a concomitant decrease of these factors in α_1-lipoprotein, from 38 to 21.3 per cent for cholesterol and from 60 to 43.5 per cent for phospholipid, without significant changes in β-lipoprotein. The alterations of α_2-lipoprotein in normals after fat intake resembled somewhat those seen in persons with idiopathic hyperlipemia on fat free diets.

The elevation of cholesterol and phospholipid in the α_2-lipoprotein fraction in idiopathic hyperlipemia exceeds by several times that seen after ingestion of fat in the normal and decreases drastically on fat free diets.

63. Effects of Dietary Imbalance on Atherogenesis in Cholesterol-Fed Cockerels

R. Pick, J. Stamler and L. N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Cockerels were fed synthetic diets in order to control intake of several dietary constituents and to study the effects of dietary imbalances on hyperlipemia and atherogenesis induced by cholesterol feeding. The following modifications were made in a cholesterol-oil supplemented synthetic basal ration (group 1): group 2, omission of methionine; group 3, choline omitted; group 4, vitamin E omitted; group 5, vitamin B_{12} and folic acid omitted; group 6, reduction of protein; group 7, increase of protein and vitamins. Compared with cockerels on commercial chick starter mash supplemented with cottonseed oil and cholesterol (group 8), the birds on the basal synthetic ration ingested less feed and gained less weight; they had less marked hyperlipemia and atherosclerosis (aortic and coronary). Deprivation of dietary methionine was associated with significant enhancement of hyperlipemia and atherogenesis (group 2 vs. group 1). Birds ingesting both the low protein and high protein rations tended to eat less food and gain less weight. The low protein birds had lesions comparable in severity to the controls (group 1). In contrast, the chicks on high-protein, high-vitamin diet exhibited markedly decreased aorta and coronary atherosclerosis. Clear-cut trends were not apparent in the other groups. These data suggest that the atherogenic effect of a cholesterol-supplemented diet is influenced by level of amino acid and protein intake. Imbalance between cholesterol-lipid and methionine ingestion apparently is particularly atherogenic, whereas protein supplementation may be protective.

64. Partial Characterization of a Lipemia Clearing Defect in Atherosclerosis

L. O. Pilgeram and L. C. Rose. From the Department of Chemistry of Stanford University, Stanford, Calif.

A method has been employed for the measurement of the activity of substances, other than clearing factor, in the lipemia clearing system of human blood. Excess canine clearing factor was incubated at 37 C. in the presence of a substrate of sesame oil and normal or atherosclerotic plasma. The rate of optical density decrease (lipemia clearing) was then followed at 700 mμ in the spectrophotometer over periods of time up to 7 hours. The complete incubation mixture contained 0.15 ml. citrated plasma, 0.1 ml. of 1 per cent sesame oil, 0.3 ml. of clearing factor (10 mg./ml. of 1:1 0.85 per cent NaCl-phos-

phate buffer [pH 7.2, Γ/2 = 0.1]) and 0.45 ml. of NaCl-phosphate buffer.

Citrated fasting plasma samples from 25 male atherosclerotics who had each sustained a myocardial infarction 6 weeks or more before the donation of the plasma sample and whose ages varied from 37 to 76 years (average 64 years) were compared to the fasting plasma samples of 22 normal young males (average 24 years). The total clearing in the pathologic plasma was only 69 per cent of the value observed for the normals.

The results of these in vitro studies demonstrate that a factor or factors, other than clearing factor, are deficient in the plasma lipemia clearing system of atherosclerotic patients *or* that a substance or substances which act as inhibitors are present in the atherosclerotic plasma.

65. Aortic Mast Cells in Man and Rabbit

O. J. Pollak. From Dover, Del.

Previously reported observations (Circulation **12:** 490, 1955.) on mast cells in the aorta have been extended. During the first decade of life mast cells are rarely seen in the human aorta; after the age of 10 years these cells are always found. There is no apparent correlation between the number of intimal-subintimal mast cells and race, sex, or age. As many mast cells are seen between yellow and white atheromatous patches as in aortas without atherosclerosis. The number of mast cells is markedly increased in edematous sectors of the aortic intima-subintima. They are present at the edges of younger plaques but not within plaques.

The original impression that aortic mast cells are numerous in patients who had died in shock has undergone revision: this seems to hold true mainly for persons who had hyperlipemia at the time of shock.

Attempts to demonstrate mast cells in the aorta of rabbits exposed to shock without or with induced hyperlipemia have failed, so far. Imitation of conditions encountered in man is difficult. Rabbits are not well suited for this study; mast cells are commonly seen in the adventitia but have never been detected in the aortic intima.

66. A Critical Dietary Factor in the Experimental Rat

*Julius Pomeranze, Sam Piliero and Ben Pansky. From the Departments of Medicine and Anatomy, The New York Medical College, Metropolitan Medical Center, New York, N. Y.**

The critical dietary factor producing hepatic, renal and cardiovascular damage in the rat is still unknown. The following experiments were undertaken to clarify the role of methyl groupings, choline and sulfur amino acids.

The diets were prepared from a basic mixture containing 18 per cent oxidized, vitamin-free casein (methionine, cystine, tryptophane and tyrosine largely removed), 2 per cent vitamin-free casein, 10 per cent α soya protein, 35 per cent corn oil, and sucrose to 100 per cent. An amino acid mixture of tryptophane and tyrosine, a 4 per cent salt mixture and a vitamin mixture were added. 1. Choline-deficient diet, methionine and cystine were added and choline was omitted from the vitamin mixture. 2. Cystine-deficient diet, methionine and choline were added. 3. Methionine-deficient diet, choline and cystine were added. 4. Methionine- and cystine-deficient diet, choline was added.

Results

There were no changes in any organs in rats fed a choline-deficient or cystine-deficient diet.

In the methionine deficient rats, there was a statistically significant gross atrophy of the testes but these organs were histologically normal and there was normal spermatogenesis. There was slight widening of the media and intima and evidence of cellular vacuolization of the aorta. The kidney showed thickening of the kidney capsule and there was occasional slight thickening of Bowman's capsule indicative of a moderate endothelial edema. The convoluted and collecting tubules showed moderate cloudy swelling and conspicuous congestion. In the liver there was focal fatty metamorphosis, periportal and centrolobular, characteristic of portal cirrhosis. There was moderate to severe pyknosis without evident mitotic activity. Central and associated slight sinusoidal engorgement was present but there was no fibrosis.

In the methionine and cystine-deficient rats, there was a marked gross testicular atrophy without accompanying histologic changes. There was some medial hypertrophy of the aorta. The kidney showed a moderate edema of the convoluted and collecting tubules. The liver displayed evidence of slight periportal fibroblastic reaction but the overall architectural pattern was well preserved. There were areas of mild microscopic hepatocellular necrosis and focal areas of fatty metamorphosis.

Conclusions

1. In the presence of sufficient protein and methionine, dietary choline deficiency produces no changes in the experimental rat as evidenced by gross, histochemical and histologic studies.

2. A cystine-deficient diet causes no changes in the experimental rat in the liver, kidney, aorta and testes.

3. Methionine deficiency with ample choline, cystine and protein produces significant changes grossly, histochemically and histologically.

4. The pathologic changes found in the experi-

* Supported by a grant from the Lipotropic Research Fund.

mental rat fed a methionine-deficient diet are different from those when sulfur amino acids are excluded from the diet (methionine- and cystine-deficient).

5. In these experiments, methionine appears to be the critical dietary factor in the rat.

67. Method for Detection of Coronary Atherosclerosis in the Living Rabbit

Seymour H. Rinzler, Janet Travell and Dorothy Karp. From the Department of Pharmacology, Cornell University Medical College, New York, N. Y.

The effect of intravenous ergonovine maleate on the electrocardiogram is useful in establishing a diagnosis of coronary insufficiency in patients with typical effort angina and a normal resting electrocardiogram (Stein test). This clinical test was applied to detect coronary atherosclerosis in the rabbit fed a 2 per cent cholesterol, 6 per cent corn oil diet. A group of 64 such cholesterol-fed rabbits (Dutch belted breed) were given serial ergonovine tests (0.05 mg./Kg. by vein) during pentobarbital anesthesia at intervals during the development of atherosclerosis. Positivity of the test was indicated by a drug-induced sagging depression of the S-T segment of at least 0.5 mm. in lead II or V_4. Two sections of the heart were examined microscopically. Correlation of the final ergonovine test with intimal changes in the coronary arteries revealed that, of 23 animals with normal coronary arteries (average 9.4 weeks on the cholesterol diet), none had a positive ergonovine test (0 per cent); of 14 rabbits with subendothelial foam cells in the coronary arteries which did not encroach on the lumen (average 9.9 diet weeks), 3 had a positive ergonovine test (21 per cent); of 27 rabbits with intimal plaques that did encroach on the arterial lumen (average 16.8 diet weeks), 20 had a positive ergonovine test (74.0 per cent). In 20 animals on a control diet, serial ergonovine tests were uniformly negative and the coronary arteries were normal. Although not all the animals with coronary atherosclerosis have a positive ergonovine test, positivity of the test does insure that coronary atherosclerosis is present.

When the ergonovine test becomes positive, the rabbit heart can be isolated and satisfactorily perfused to study the actions of drugs on the atherosclerotic heart, and the degree of intimal changes in the arteries can be verified pathologically after perfusion.

68. The In Vitro Effect of Soybean Phosphatides on Serum Lipoproteins of Normal and Hyperlipemic Subjects

Bernard A. Sachs and Ethel Danielson. From the Medical Division of Montefiore Hospital, New York City, N. Y.

Aliquots of the postabsorptive sera of 6 normal and 5 hyperlipemic subjects were analyzed for protein and lipid by paper electrophoresis before and after mixture with a purified extract of natural soybean phosphatides, containing approximately equal amounts of lecithin, cephalin and lipositol. Another aliquot of each serum and serum phosphatide mixture was incubated at 37 C. for 24 hours and then subjected to electrophoretic analysis. The unincubated sera demonstrated little or no change when compared to the phosphatide-free controls. However, all of the phosphatide-containing incubated sera, both normal and hyperlipemic, showed an increase in the migration velocity of β-lipoprotein, i.e., lipoprotein associated with β-globulin migrated to the region between α_2- and α_1-globulin. In addition, 5 of the 6 normal sera and 1 of the 5 hyperlipemic sera demonstrated a definite but milder increase in the migration velocity of the lipid-staining band associated with α_1-globulin and albumin (α-lipoprotein) to an area on the strip immediately beyond albumin.

To evaluate further the "lipoprotein shift" observed, the alcohol-soluble fraction of the soybean phosphatide, containing approximately two-thirds lecithin and one-third cephalin, and the alcohol-insoluble fraction, containing approximately two-thirds lipositol and one-third cephalin, were tested in a similar manner with the sera of 10 normal and 9 hyperlipemic subjects. After incubation, the alcohol-soluble fraction produced little or no change in the serum lipoproteins. However, the alcohol-insoluble fraction produced an increase in migration velocity similar to that demonstrated with the whole soybean phosphatide complex. These data suggest that lipositol probably is the compound responsible for the changes in the migration velocities of the serum lipoproteins produced by soybean phosphatides. These changes are similar to those produced by heparin in vivo and by "clearing factor" in vitro.

The heparin effect has been shown to be due to the liberation of free fatty acids. To determine whether the mechanism of action is the same for the soybean phosphatides, free fatty acids were determined on sera incubated with the alcohol-soluble or alcohol-insoluble fractions. Preliminary studies reveal the presence of increased amounts of free fatty acids in the sera incubated with either fraction as compared to control sera. However, no significant difference was found in the amounts of free fatty acids liberated by the alcohol-insoluble fraction as compared to the alcohol-soluble fraction. Therefore, the mechanism of action of the lipoprotein shift produced by the lipositol has not been clarified as yet. Preliminary studies on the in vivo effect of the alcohol-insoluble fraction in man have also been carried out.

69. Correlation between Lipfanogens and Lipoproteins

Henry S. Simms, Frank T. Lindgren, Charles R. Harmison and Alex V. Nichols. From Columbia University, New York, N. Y., and the University of California, Berkeley, Calif.

Although we have previously shown that the lipfanogens are not identical with the lipoproteins, we undertook to determine whether there is a correlation between these agents.

In a joint study of sera from 25 clinically "normal" adult males, we find evidence that the S_f 20–400 lipoproteins have a positive correlation with the free lipfanogens ($r = +0.57$, $p = 0.01$) and an inverse correlation with the free antilipfanogen ($r = -0.41$, $p = 0.05$).

The free lipfanogens (which were determined by the fat-depositing action of unheated serum on tissue cultures under standard conditions) ranged from 6.4 units to 20.0 units. The free antilipfanogen (which was computed from the fat-depositing action of both heated (at 90 C.) and of unheated serum) ranged from 6.9 to 25.0 units. The range of the S_f 20–400 lipoproteins was from 76 to 803 mg./100 ml. At the same time there was a range of S_f 0–12 lipoproteins from 137 to 454 mg./100 ml. and of S_f 12–20 from 22 to 112 mg./100 ml. but these did not correlate with the lipfanogens.

At the same time the total high density lipoproteins (185 to 429 mg./100 ml.) appear to have some degree of direct correlation with the free antilipfanogen ($r = +0.34$, $p = <0.2$), as well as an inverse relationship with the free lipfanogens ($r = -0.36$, $p = 0.1$).

SPECIAL ANNOUNCEMENTS

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

ANNUAL MEETING

GUEST LECTURER:

Sunday, November 11,
Luncheon 12:00 Noon

Donald Mainland, Professor of Medical Statistics, New York University College of Medicine

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RECEPTION FOR THE TEN PAST PRESIDENTS AND THEIR LADIES

Sunday, November 11,
6:30–7:30 P.M.

Dress—Semi-Formal

LUNCHEONS:

Sunday, November 11,
12:00 Noon

Monday, November 12,
12:00 Noon

ANNUAL BUSINESS MEETING:

Sunday, November 11,
2:00 P.M.

Presidential Address,
2:30 P.M.

Ladies are invited to register Sunday, before 10:00 A.M.

All activities take place at The Palmer House, Chicago

CONTRIBUTORS TO THIS ISSUE

WILLIAM L. ALSOBROOK, M.D.

Director, Professional Services, Thayer Veterans Administration Hospital; Instructor in Clinical Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

CLIFFORD W. ATHERTON. M.D.

Assistant Chief, Laboratory Service, Thayer Veterans Administration Hospital, Nashville, Tenn.

LUIS M. BECU, M.D.

Research Assistant, Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minn.

ALBERT BEHREND, M.D.

Attending Surgeon, Albert Einstein Medical Center; Assistant Professor of Surgery, Temple University School of Medicine, Philadelphia, Pa.

MAURICE M. BEST, M.D.

Assistant Professor of Medicine, University of Louisville School of Medicine, Louisville, Ky.

LEON BLUMBERG, M.D.

Assistant, Medical Service, Albert Einstein Medical Center, Philadelphia, Pa.

ROBERT W. BUCK, M.D.

Secretary, Massachusetts Medical Society, Boston, Mass.

HOWARD B. BURCHELL, M.D.

Consultant, Section of Medicine, Mayo Clinic; Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

WILLIAM D. COHEN, PH.D.

Research Biochemist, The Memorial Hospital, Worcester, Mass.

JØRN DITZEL, M.D.

Research Associate, Baker Clinic Research Laboratory, New England Deaconess Hospital, and the Joslin Clinic, Boston, Mass.

CHARLES H. DUNCAN, M.D.

Assistant Professor of Medicine, University of Louisville School of Medicine, Louisville, Ky.

JAMES W. DUSHANE, M.D.

Consultant, Section of Pediatrics, Mayo Clinic; Assistant Professor of Pediatrics, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

JESSE E. EDWARDS, M.D.

Consultant, Section of Pathologic Anatomy, Mayo Clinic; Professor of Pathologic Anatomy, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

ROBERT S. FONTANA, M.D.

Fellow in Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

RICHARD FRANCE, M.D.

Chief, Medical Service, Thayer Veterans Administration Hospital; Associate Professor of Clinical Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

BENJAMIN GAZUL, M.D.

Clinical Professor of Pediatrics, Northwestern University Medical School, Chicago, Ill.

ROBERT S. GREEN, M.D.

Director, Memorial Heart Laboratory and Clinics, St. Mary's Hospital, Cincinnati, Ohio; Instructor in Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

DONALD HEATH, M.D.

Lecturer in Pathology, University of Birmingham, England; Formerly Leverhulme Research Scholar, Royal College of Physicians, London.

ROBERT HERSHBERGER, M.D.

Senior Fellow in Cardiology, Houston Heart Association, Jefferson Davis Hospital, Houston, Tex.

NORIO HIGANO, M.D.

Assistant Physician, Medical Division; Physician-in-Charge, Radioisotope Research Laboratory; Clinical and Research Associate in Medicine, The Memorial Hospital, Worcester, Mass.

ARNOLD IGLAUER, M.D.

Assistant Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

URSULA JEGHER

Laboratory technician, University of Louisville Institute for Medical Research, Louisville, Ky.

JOHN W. KIRKLIN, M.D.

Consultant, Section of Surgery, Mayo Clinic; Assistant Professor of Surgery, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

DANIEL S. KUSHNER, M.D.

Associate Director of Medical Education, Cook County Hospital; Research Associate at Hektoen Institute for Medical Research of Cook County Hospital; Instructor in Medicine, Northwestern University Medical School, Chicago, Ill.

GEORGE MORRIS, M.D.

Chief Resident in Surgery, Jefferson Davis Hospital, Houston, Tex.

JOHN H. MOYER, M.D.

Associate Professor of Medicine and Pharmacology, Baylor University College of Medicine; Associate Physician, The Methodist and Jefferson Davis Hospitals; Attending Physician, Houston Tuberculosis Hospital and the Veterans Administration Hospital, Houston, Tex.

GEORGE A. PERERA, M.D.

Associate Professor of Medicine, Columbia University College of Physicians and Surgeons; Associate Attending Physician, Presbyterian Hospital and Vanderbilt Clinic, New York, N. Y.

ROBERT PONTIUS, M.D.

Instructor in Surgery, Baylor University College of Medicine, Houston, Tex.

HANS POPPER, M.D.

Director of Department of Pathology, Cook County Hospital; Scientific Director of the Hektoen Institute for Medical Research of Cook County Hospital; Associate Professor of Pathology, Northwestern University Medical School, Chicago, Ill.

JOSEPH E. F. RISEMAN, M.D.

Assistant Clinical Professor of Medicine, Harvard Medical School; Instructor of Medicine, Tufts Medical School; Visiting Physician, Beth Israel Hospital, Boston, Mass.

ROGER W. ROBINSON, M.D.

Chief of Medical Division; Director of Research Laboratory, The Memorial Hospital, Worcester, Mass.

IAN E. RUSTED, M.D.

Fellow in Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

WM. R. SCARBOROUGH, M.D.

Assistant Professor of Medicine, Johns Hopkins Medical School and Hospital; Research Associate, Howard Hughes Medical Institute, Baltimore, Md.

RALPH C. SCOTT, M.D.

Fellow in Internal Medicine (Cardiac Laboratory), Cincinnati General Hospital; Assistant Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

CHARLES H. SCHEIFLEY, M.D.

Consultant, Section of Medicine, Mayo Clinic; Assistant Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

JOSEPH W. SHERER, JR., M.D.

Assistant Urologist, Surgical Division, The Memorial Hospital, Worcester, Mass.

RONALD C. SNIFFEN, M.D.

Pathologist, The Memorial Hospital, Worcester, Mass.; Associate Visiting Pathologist, Massachusetts General Hospital; Instructor in Pathology, Harvard Medical School, Boston, Mass.

SAMUEL A. TALBOT, PH.D.

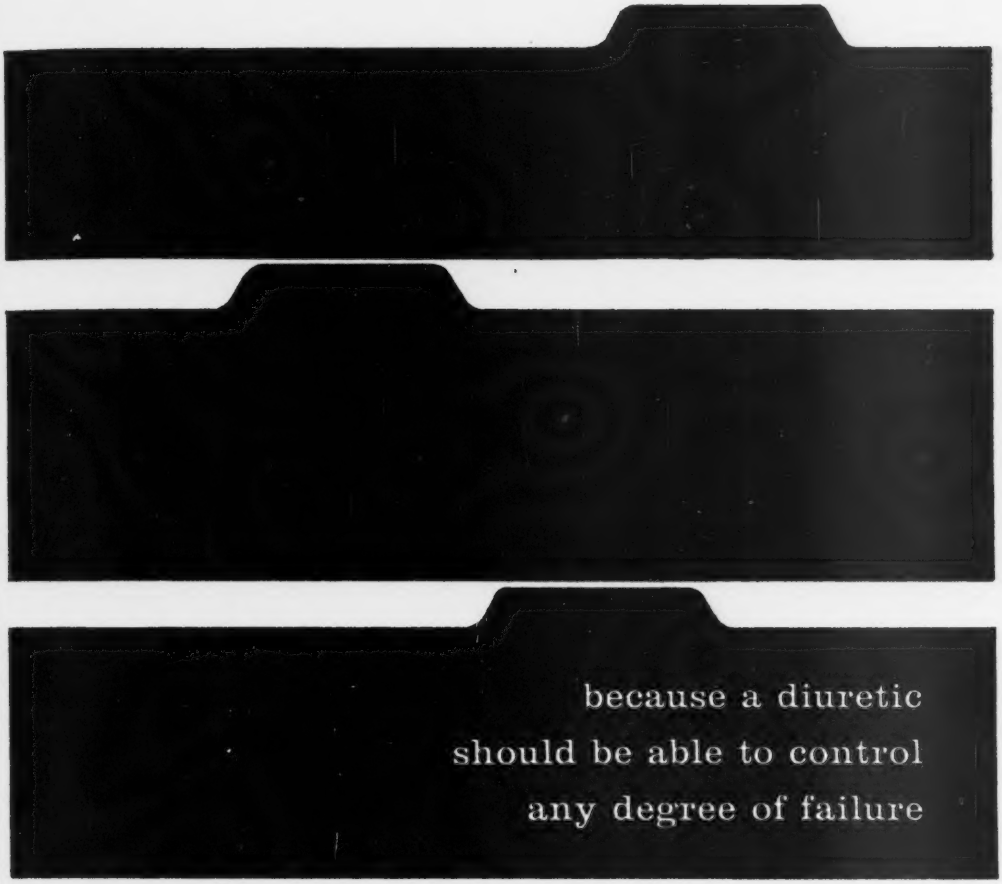
Biophysicist, Associate Professor of Medicine, Johns Hopkins Medical School, Baltimore, Md.

JOAN D. WATHEN, B.S.

Biochemist, University of Louisville Institute for Medical Research, Louisville, Ky.

W. WHITAKER, M.D., B.SC., M.R.C.P.

Assistant Physician (Cardiological), The General Infirmary at Leeds; formerly Senior Lecturer in Medicine, University of Sheffield, England.



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